

The Alkyl Benzenes

Committee on Alkyl Benzene Derivatives

Board on Toxicology and Environmental Health Hazards

Assembly of Life Sciences

National Research Council

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PREFACE

The Committee on Alkyl Benzene Derivatives of the Board on Toxicology and Environmental Health Hazards (BOTEHH), Assembly of Life Sciences, National Research Council, was established to assist the BOTEHH in complying with Contract No. 68-01-4655 with the U.S. Environmental Protection Agency (EPA). The committee was charged with the responsibility for assessing the health effects and the environmental impact of the alkylated benzenes and with submitting a report of its findings to the EPA. The EPA is expected to use the assessment as a basis for developing regulations.

The committee selected topics that pertain to either individual alkyl benzenes or to the group of compounds as a unit. This process ultimately defined the scope of the report and clearly defined essential sections of the report that were to be approached by the various committee members.

Because of the potential necessity to assess the effects on human health as well as on the environment at large from the compounds, the committee was asked to review the sources and uses of these compounds, their chemical and physical properties, and aspects of their chemistry that would pertain to their uses in industry. The charge also called for an assessment of techniques for sampling and measuring the levels of these compounds in the environment, the role played by their chemistry in their transport, and how their chemistry could relate to the effects they produce. The EPA required the inclusion of an analytical section that would examine the most relevant measurement techniques for determining ambient levels of the alkyl benzenes in various transport media and, to the extent possible, comment on instrumentation and availability of reference compounds for standardizing the instruments. These aspects are addressed in Chapters 1, 2, and 3 of the report.

Of perhaps greatest significance in this document are the sections covered in Chapter 4, which are devoted to occurrence and transport of the compounds in the environment and mechanisms and extent of environmental exposure. Chapter 5 describes metabolism in mammalian and nonmammalian species. Chapters 6 and 7 contain a careful evaluation of the fundamental aspects of the toxicology of each of these chemicals in mammals, estimates of the hazards associated with their occurrence, and an assessment of evidence for the potential mutagenic and/or carcinogenic activity of these compounds. Chapter 8 is devoted to the effects of these compounds in nonmammalian species. Finally, in Chapter 9, the committee summarizes its findings, presents general recommendations for future research, and highlights areas that deserve particular attention.

The committee regrets that it was unable to obtain information on the technology that is currently used to control the emissions of these compounds. The available information could permit only some preliminary judgments regarding the economic impact of such controls (Chapter 1). Because of the lack of sufficient data, the committee encountered similar difficulty in attempting to assess the carcinogenic risk of these compounds, and opted against it.

Looking back over the written contributions of the members, the judgments made at meetings, and their ability to work together effectively to reach joint conclusions, I must compliment them on a successful collaborative effort. Since they are scientists recognized as leaders in their individual fields, it was necessary for them to spend some time away from their research for this work. They can take comfort in the fact that their efforts will play a major role in the development of controls for environmental exposure to these chemicals. I am delighted to have the opportunity to work with them.

This effort would not have been possible without the untiring efforts of Dr. Sushma Palmer, Staff Officer for the Board on Toxicology and Environmental Health Hazards (BOTEHH), who supervised the efforts, provided all necessary logistical support, and did whatever was necessary to ensure success in this endeavor. We would also like to acknowledge the overall direction of Dr. Robert G. Cluff whose judgment and enthusiasm has played a major role in the success of BOTEHH and its Committee on Alkyl Benzene Derivatives. This report could not have been prepared without the invaluable secretarial assistance of Susan Barron, Dena Banks, and Eileen Brown.

The committee also wishes to acknowledge the contribution of the following individuals who supplied significant information and documents for the committee's use and served as consultants during various phases of the study: Charles E. Holdsworth and Carl K. Weaver, American Petroleum Institute; Ralph Wands, Mitre Corp.; Randal P. Schumacher, Chemical Manufacturers Association; David W. Hazelton, Consultant; William O. Berry, Department of the Air Force, Bolling Air Force Base; John Quast and John Ramsey, Dow Chemical Company; D. Bauer, F. Hoffmann-La Roche & Co.; Robert E. Miles, Haskell Laboratory for Toxicological & Industrial Medicine, E. I. du Pont de Nemours & Co.; Ch. Schlatter, Institut Für Toxikologie, Eidgenössischen Technischen Hochschule und der Universität, Zürich; Joseph E. Hadley, Jr., Keller and Heckman; Julianne B. Harvey, Chemical Manufacturers Association; Tom Haley, National Center for Toxicological Research; Peter Nawrot, National Institute for Environmental Health Sciences; George Hoffmann, National Research Council; Edo D. Mazzari, Research Triangle Institute; Ronald W. Wood, University of Rochester Medical Center; John Bachmann, Alan Carlin, Edward Cull, John Fry, Robert J. M. Horton (retired), Richard Johnson, S. D. Lee, John Shaughnessy, and Gunter Zweig, U.S. Environmental Protection Agency; Louis De Toro, U.S. International Trade Commission; and

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INTRODUCTION

The alkyl benzenes are single ring aromatic hydrocarbons with a variety of aliphatic side chains attached to the ring. Toluene, ethylbenzene, and cumene contain methyl, ethyl, and isopropyl groups, respectively. When the ring contains two methyl groups, there are three possible isomers: 1,2-, 1,3-, and 1,4- dimethylbenzene. These constitute the three components of the xylenes. The addition of a vinyl group produces styrene, whereas epoxidation of the vinyl group yields styrene oxide. Both styrene and its oxide are strictly synthetic chemicals that are used in the manufacture of polystyrene plastics.

There are literally hundreds, if not thousands, of alkyl derivatives of benzene; however, in its initial evaluation of structures that fall into this category, the committee identified approximately 30 structures that may be potentially hazardous. For this report, the list was further reduced to the six compounds listed above because they are the most widely produced alkyl benzenes and because they are the only alkyl benzenes for which there is sufficient toxicological literature for the committee to develop a reasonable summary of their biological and environmental effects.

These chemicals are liquids with relatively low boiling points. They are used as solvents or as intermediates in synthetic chemical processes. Their primary source is the petroleum industry and, to a lesser extent, the coke industry. Their role in the manufacture of plastics accounts for much of their use, and their addition to gasoline as an antiknock replacement for lead has given them added economic importance in the chemical industry.

The first tenet of the discipline of toxicology was pronounced by Paracelsus, who admonished that the dose makes the poison. Although the toxic effects of a chemical can be described, the hazard associated with exposure to the chemical is a function of the dose. These concepts are important to the assessment not only of chemicals that exert adverse effects at low doses, and are therefore toxic under most ordinary conditions, but also of less potent agents that are produced in large quantities. Many alkyl benzenes fall into the latter category since their toxic properties are generally exerted at high levels of exposure, and they are produced in such massive quantities that potential exposure to these compounds is considerably greater than if they were merely laboratory curiosities. According to the U.S. International Trade Commission, the 1979 production of toluene, ethylbenzene, cumene, the xylenes, and styrene was approximately 6.4, 36.0, 16.0, 4.0, and 30.0 billion liters, respectively. As a result of production, usage, and eventual disposal, there is a high probability that humans as well as plants and animals will be exposed

these compounds. Furthermore, it is likely that some of the organisms will be exposed to quantities of sufficient concentrations to produce adverse effects.

Although these chemicals are relatively impotent toxic agents and do not appear to represent a serious carcinogenic hazard, their ubiquitous presence in the environment and the potential that large numbers of humans may be exposed to them suggest that we must continue to refine our knowledge of their toxicities and the circumstances in which they may pose an environmental hazard. Although the degree to which environmental emissions of these agents should be controlled is not clear at this time, the committee hopes that this report will be of value to regulatory officials charged with determining criteria to safeguard the public.

CHAPTER 1

SOURCES, USES, EMISSIONS, AND CONTROLS

The vast majority of the alkyl benzenes produced for commercial use throughout the world are derived directly or indirectly from petroleum (Brownstein, 1976) and, to a much lesser extent, from their occurrence as by-products of coke-oven operation. Substantial amounts of these materials, which are called "native" compounds, occur naturally in crude petroleum. Some are formed by the breaking apart of high molecular weight crude oil molecules during catalytic cracking, although the majority of the toluene and xylenes are produced from C₇ and C₈ cycloalkanes (naphthenes) and n-alkanes (n-paraffins) in a petroleum refining process called catalytic reforming. Cumene and ethylbenzene are produced for chemical use by alkylation of benzene with propylene and ethylene, respectively, and almost all of the styrene comes from dehydrogenation of ethylbenzene. Styrene oxide is not prepared in large quantities for commercial use; however, it is the primary product of styrene metabolism.

Well over half of all the alkyl benzenes produced are used as blending stocks for gasoline to increase the octane number of the fuel. Only a relatively small amount is isolated and recovered for use in the chemical industry. Unfortunately, most of the "production" figures given in the literature, such as those shown in Table 1-1, are based on chemical usage, which represents only a small fraction of the compounds actually consumed. Table 1-2 shows the fraction of the available benzene, toluene, and the xylenes that are used by the chemical industry. Table 1-3 contains historical data for toluene production and consumption since 1960.

In the United States alkyl benzene compounds are ubiquitous constituents of the environment, especially of urban air. Their use as major components of fuel for automobiles, trucks, and airplanes, as solvents in cleaning preparations, paints, adhesives, and other coatings, and as chemicals that are integral to a variety of industrial processes insures their presence in the atmosphere near centers of human activity. Their use in gasoline has been expanded recently by the exclusive production of catalyst-equipped automobiles in the United States. Unleaded gasoline, which is required for these vehicles, is generally richer than regular or premium grades in alkyl benzene content. The environmental pollution resulting from the increase in this use has been offset by the catalytic converters, which reduce the emissions of hydrocarbons from modern automobiles.

Since environmental controls are decreasing the transportation-related emissions of alkyl benzenes, a larger proportionate contribution to atmospheric hydrocarbon levels could be expected from the wide application of these compounds in solvents.

TABLE 1-1. U.S. Production of Selected Alkyl Benzenes^a

Compound	Amounts Produced, millions of metric tons, by year					
	<u>1974^b</u>	<u>1975^b</u>	<u>1976^c</u>	<u>1977^c</u>	<u>1978^c</u> <u>(preliminary)</u>	<u>1979^d</u>
Benzene	3.0	2.3	3.2	3.3	4.1	6.4
Toluenes	2.6	2.1	2.5	2.8	2.7	3.7
Ethylbenzene	3.2	2.5	2.6	3.8	3.8	3.9
Isopropylbenzene (cumene)	1.3	0.91	1.2	1.2	1.5	1.8
Styrene	2.7	2.1	2.9	3.1	3.1	3.4

These figures are based on the chemical industry, but do not include most of the alkyl benzenes in gasoline or mixed solvents.
Stanford Research Institute, 1977.

S. International Trade Commission, 1977.

S. International Trade Commission, 1980.

TABLE 1-2. Total Amount of Aromatics Produced in the United States
and the Total Amount Used by Chemical Industries in 1974^a

<u>Aromatic</u>	<u>Quantity</u>		<u>Million Metric Tons/Year</u>
	<u>%</u>	<u>Barrels/day</u>	
Crude oil processed	100	14,216,000	608.6
Available benzene	0.68	97,000	4.2
Chemical benzene market	0.54	76,680	3.9
Available toluene	2.3	326,968	14.0
Chemical markets	0.30	42,500	1.8
Available xylenes	2.5	355,400	15.3
Chemical markets	0.24	34,250	1.5

^aFrom Brownstein, 1976.

TABLE 1-3. Toluene "Produced" and Present in Crude Oil and Gasoline Consumed in the United States^a

	Quantity of toluene, million metric tons		
	<u>In crude oil^b</u>	<u>In automobile gasoline^c</u>	<u>"Produced"^d</u>
1983	4.4	NA ^e	4.1
1977	4.4	22	3.3
1966	4.0	22	3.2
1955	3.7	21	2.3
1940	3.3	18	NA
1930	2.4	11	NA

^a Consumption data from U.S. Bureau of the Census, 1979.

^b Calculated as 0.5% of U.S. crude oil consumption (see data in Table 1-4).

^c Estimated as 7% of total U.S. automobile gasoline consumption (Table 1-9). Does not include diesel and aviation consumption. From Table 1-1.

^d Data not available.

NATIVE ALKYL BENZENES

As shown in Table 1-4, unfractionated crude oil contains between 1% and 2.5% by weight C_6 - C_8 aromatics--mainly toluene and the xylenes plus ethylbenzene (Brownstein, 1976). Almost all of these compounds can be recovered in an intermediate naphtha fraction by distillation between 65°C and 150°C. Since this fraction usually represents only 10% to 20% of the starting crude oil, it is possible to obtain from 5% to 25% yields of native alkyl benzenes in the naphtha fraction. In addition, most of the crude oil content of C_6 - C_9 naphthenes, which are present in levels from 1 to 4 times these amounts, can be converted into aromatics through catalytic reforming.

CURRENT COMMERCIAL PRODUCTION TECHNIQUES

Catalytic Reforming

Through this process, low octane, heavy gasoline can be upgraded into high octane fuel with good antiknock qualities, suitable for use in high compression ratio gasoline engines. This upgrading is accomplished mainly by the conversion of aliphatic and naphthenic (nonaromatic) compounds in the C_6 to C_9 range into aromatics. In this process, desulfurized naphtha is fed (along with hydrogen at 300-700 psig) into a series of three to five fixed-bed reactors filled with a platinum-based catalyst operating at 315°C to 425°C (Figure 1-1). Interstage heaters located just upstream from each reformer provide the required heat for the endothermic reactions, which include dehydrogenation of cyclic paraffins (e.g., methylcyclohexane converted to toluene plus hydrogen) and dehydrocyclization of paraffins with at least six carbon atoms in a straight chain (e.g., n-heptane converted to toluene plus hydrogen). Although the dehydrogenation reactions are essentially quantitative, the dehydrocyclization reactions are more difficult and are usually accompanied by undesirable side reactions, such as hydrogenolysis (hydrocracking), which form methane, ethane, propane, and butane. The degradation reactions increase with the severity of operating conditions, e.g., higher temperatures and longer contact times in the reactor, which are required to produce higher octane fuel. A decrease in the yield of reformat, a product that is used in gasoline, results (Figure 1-2).

Extensive research is underway to develop more selective catalysts (most of which contain platinum plus other noble or transition metals supported on porous alumina) that will maximize the desired reactions while minimizing hydrogenolysis. A novel catalyst developed by researchers at Mobil Oil contains tellurium mixed with a sodium X-zeolite (Miale and Weisz, 1971; Price et al., 1980). This catalyst is highly selective for converting n-paraffins into aromatics without isomerizing the carbon skeletons.

TABLE 1-4. Occurrence of Aromatics and Aromatic-Forming Cycloparaffins in Various Crude Oils^a

Compound	Percentage, by Source					
	Louisiana Gulf	West Texas	Venezuela	Libya	Nigeria	Iran
Naphtha at 66°C-149°C	13	18	10	17	17	15
Total C ₆ -C ₈ aromatics:						
in crude	1.1	1.79	1.85	1.0	2.50	1.80
in naphtha	8.5	11.0	18.5	5.8	20.7	12.0
Benzene, in crude	0.15	0.18	0.15	0.07	0.11	0.19
Toluene, in crude	0.45	0.51	0.60	0.37	0.92	0.56
C ₈ aromatics in crude	0.50	1.10	1.10	0.56	1.47	1.05
Total C ₆ -C ₈ naphthenes in crude	3.87	6.37	3.4	2.50	7.2	2.92
Benzene precursors in crude	0.67	0.97	0.50	0.55	1.2	0.65
Toluene precursors in crude	1.3	2.0	1.6	1.05	3.5	1.19
C ₈ aromatics precursors in crude	1.9	3.4	1.3	0.90	2.5	1.08

^aFrom Brownstein, 1976.

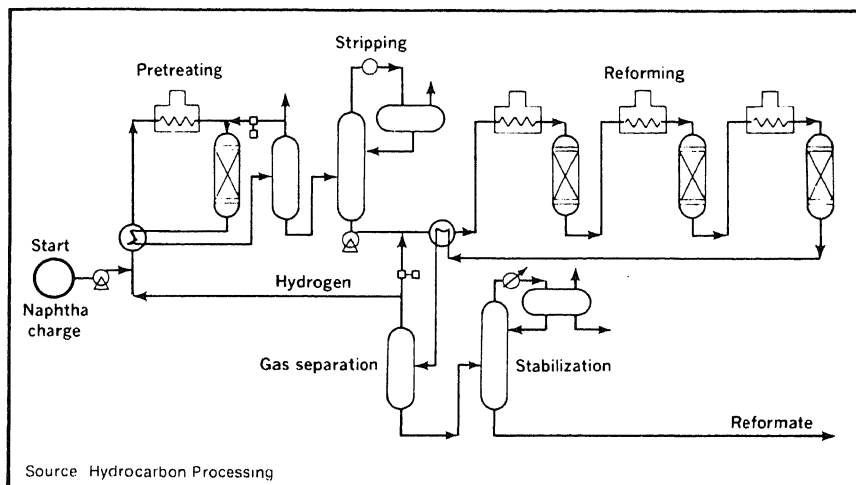


FIGURE 1-1. Scheme for a typical catalytic-reforming plant.
From Brownstein, 1976.

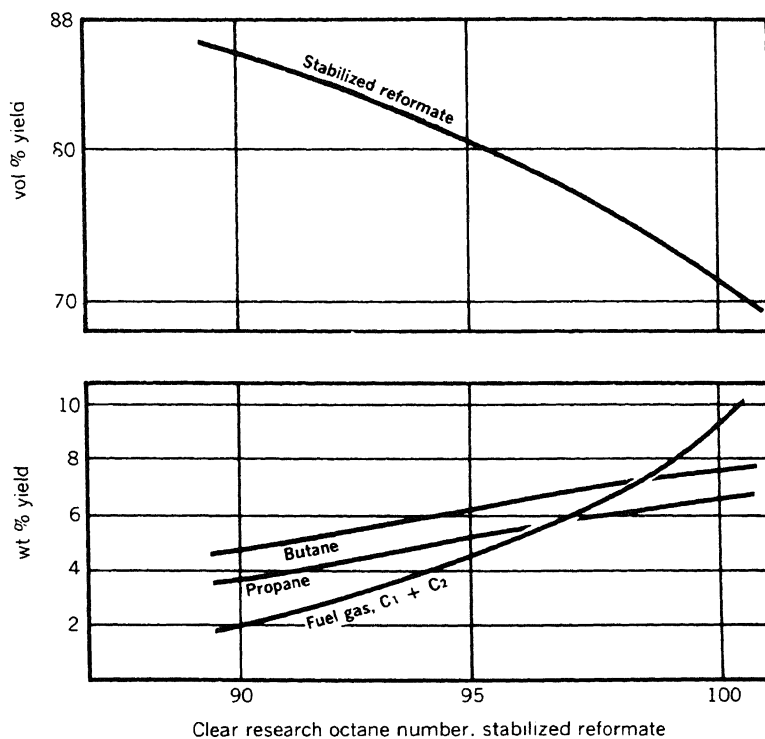


FIGURE 1-2. Reformat yield as a function of octane number. From Brownstein, 1976.

5 shows the yield of aromatics in typical reformat as the severity of operating conditions, especially temperature and pressure. The increase in octane number with increase in quantity of aromatics in the reformat, this increase is accompanied by a decrease in the yield of a correspondingly greater production of lightweight aromatics such as those seen in Figure 1-2. All the alkyl benzenes in this study (except styrene oxide) have research octane numbers in excess of 100 (Table 1-6). Table 1-7 shows the results after a typical naphtha has been reformed to a research octane number in the range of 93 to 95 RON. The reformat is usually blended with material from other refinery streams to bring it in the desired octane range. Table 1-8 shows the aromatic content of various gasolines. Table 1-9 provides a breakdown of individual alkyl benzenes in a composite sample from the Los Angeles area.

A greater quantity of aromatics in gasoline is likely to be required in the future to meet the increasing relative demand for high octane fuel despite the predicted decline in total gasoline consumption. Table 1-10 shows the projected 10-year schedule for the use of leaded gasolines, both premium and regular, and the required switchover to 100% unleaded fuel by 1985. There is considerable uncertainty about whether or not the timetable in Table 1-10 will be enforced since it is being challenged in the United States National Petroleum Refiners Association and several states to restrict tetraethyl lead.

Catalytic reforming capacity in the United States has increased markedly since 1960 (Figure 1-3). It is also apparent that the percentage of crude oil that is subjected to reforming and the refining process has been increasing (Figure 1-4).

Gasoline

Ethylene and propylene are very important building blocks in the production of many different kinds of plastics. A significant part of the formation of these olefins is steam cracking. Along with the olefins, a small amount of "drip oil," or pyrolysis gasoline, is produced. This product is very rich in aromatics. The current practice is to steam crack heavier feeds such as naphtha and gas oil to produce the olefins. Such feedstocks yield considerably more aromatic gasoline. For example, a typical plant, which produces one million metric tons of ethylene annually using gas oil as feedstock, will produce 8,000 to 10,000 barrels (approximately 1,000 metric tons) of pyrolysis gasoline daily (Brownstein, 1974). This is not at all unusual for this pyrolysis gasoline to

TABLE 1-5. Yield of Aromatics as a Function of Severity of Reformer Operation^{a,b}

<u>Final Octane Range (RON)^c</u>	<u>C₅+ Reformate, vol % Feed</u>	<u>Aromatics, vol % of Reformate</u>	<u>Fuel Gas and Light Ends, vol % Feed</u>
89-91	85	48	15
93-95	80	55	20
99-101	72	66	28

^aFrom Brownstein, 1976.

^bOperating conditions refer mainly to changes in temperature and pressure.

^cRON = research octane number.

TABLE 1-6. Research Octane Number (RON) for Several Alkyl Benzenes^a

<u>Compound</u>	<u>RON</u>
Benzene	108
Toluene	112
Ethylbenzene	113
<u>p</u> -Xylene	114
<u>m</u> -Xylene	114
<u>o</u> -Xylene	100
Typical C ₉ .mix	103

^aFrom Brownstein, 1976.

TABLE 1-7. Typical Aromatic Content of Reformate^a

<u>Compound</u>	<u>Reformate, vol %</u>
Benzene	5
Toluene	24
Ethylbenzene	4
<u>p</u> -Xylene	4
<u>m</u> -Xylene	9
<u>o</u> -Xylene	5
C ₉ and C ₁₀ aromatics	<u>4</u>
TOTAL	55

^aFrom Brownstein, 1976.

TABLE 1-8. Alkyl Benzenes in Gasoline

Type of Gasoline	Percentage of Alkyl Benzene Compounds				
	1969 ^a	1970 ^b	1970 ^c	1974 ^d	1978 ^e
Unleaded	NR ^f	41	NR	NR	38
Premium	29	39	27	NR	33
Regular	NR	31	NR	NR	31
Composite	NR	NR	NR	21	35

^aMaynard and Sanders, 1969.^bMayrsohn and Bonamassa, 1971.^cMorris and Dishart, 1971.^dMyers et al., 1975.^eMayrsohn et al., 1978.^fNot reported.

TABLE 1-9. Individual Alkyl Benzenes Found in a Composite Gasoline Sample Obtained in Los Angeles^a

Compound	Percent by weight	Compound	Percent by weight
benzene	1.34	1,2-Diethylbenzene	0.57
toluene	6.73	1,3-Diethylbenzene	0.08
ethylbenzene	1.71	1,3-Dimethyl-2-ethylbenzene	0.59
m- and p-Xylene	6.73	1,2,4,5-Tetramethylbenzene	0.37
o-Xylene	2.86	1,2,3,5-Tetramethylbenzene	0.15
cumene (isopropylbenzene)	0.14	Naphthalene	0.46
propylbenzene	0.61	TOTAL	32.10 ^b
o-Ethyltoluene	0.96		
m- and 4-Ethyltoluene	2.89		
1,2,4-Trimethylbenzene	3.30		
1,3,5-Trimethylbenzene	1.15		
isobutylbenzene	0.44		
isobutylbenzene	0.08		
sec-Butylbenzene	0.09		
tert-Butylbenzene	0.12		
1-Methyl-3-N-propylbenzene	0.56		
1-Methyl-4-isopropylbenzene	0.02		
1-Methyl-2-N-propylbenzene	0.15		

^aFrom Mayrsohn et al., 1978.

^bUnidentified alkyl benzenes would probably raise this figure to approximately 35%.

TABLE 1-10. EPA Schedule for Removing Lead from Gasoline^a

<u>Year</u>	<u>Percent of total sales, by type of gasoline</u>		
	<u>Regular</u>	<u>Premium</u>	<u>Unleaded</u>
1974	73	22	5
1975	66	19	15
1976	55	15	30
1977	44	12	44
1978	37	10	53
1979	30	7	63
1980	23	5	72
1985	0	0	100

^aFrom Brownstein, 1976.

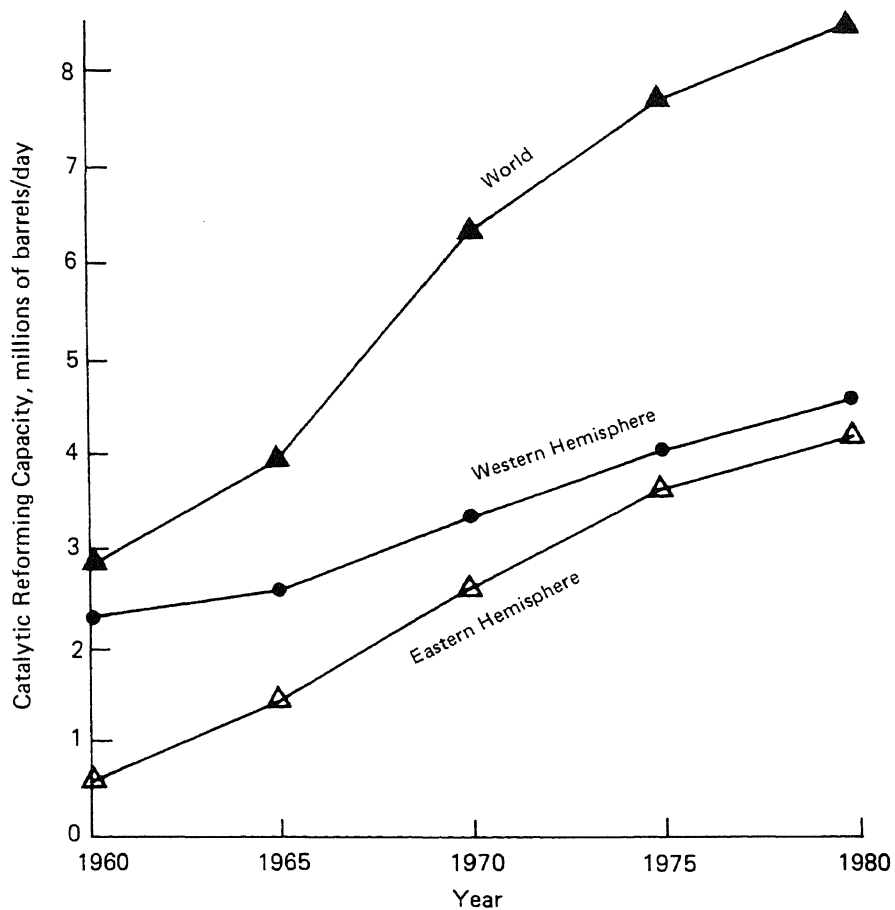


FIGURE 1-3. Daily catalytic reforming capacity in petroleum refining. Data from Universal Oil Products Company, personal communication.

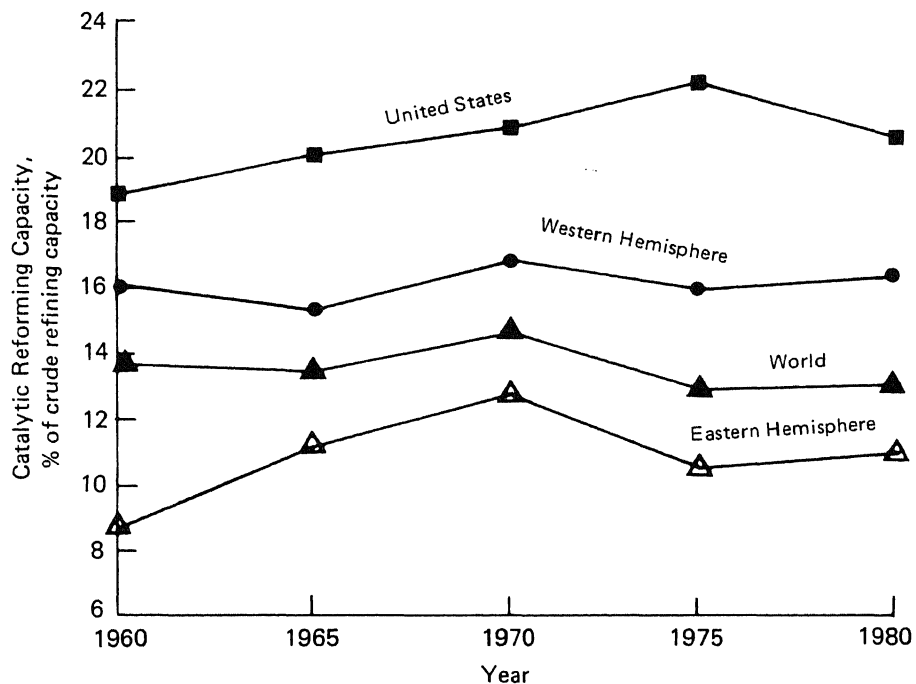


FIGURE 1-4. Catalytic reforming capacity, as a percentage of crude-oil refining capacity. Data from Universal Oil Products Company, personal communication.

contain 70 weight percent aromatics, approximately half of which is benzene and half of which is mainly toluene and the xylenes. Since more steam cracking plants use heavier feedstocks, this source of aromatics will undoubtedly increase during the next few years. The pyrolysis gasoline also contains approximately 8% monoolefins and 15% diolefins, both of which are normally hydrogenated in a two-step process (Figure 1-5, Brownstein, 1976).

Purification of Alkyl Benzenes

Separation of the aromatics from paraffins in raffinate is relatively simple. This is normally accomplished by extraction with solvents using either a Udex process (Figure 1-6, Brownstein, 1976) with di- and triethyleneglycol or the Sulfolane process with tetrahydrothiophene dioxide as the solvent for the aromatics. Once separated from the paraffins, the aromatics can be separated further into molecular weight groups in a series of simple distillation columns such as those shown in Figure 1-7 (Brownstein, 1976). By this technique it is possible to produce streams of benzene, toluene, and the mixed xylenes plus ethylbenzene that are greater than 99% pure. The clay towers are used to remove traces of olefins and sulfur compounds.

Typical percentages present in the stream of C_8 aromatics are given in Table 1-11 (Brownstein, 1976). Purification of the individual xylenes and ethylbenzene is difficult due to their similar physical properties, e.g., all the C_8 aromatics have boiling points that lie between 136.2°C and 144.4°C. Separation of all the compounds by distillation is not practical. However, it is possible to isolate 95+% pure o-xylene as "bottoms" (material accumulated at the bottom of a distillation column because of its high boiling point) from a 100-tray, 150- to 200-foot column operated with reasonable reflux ratios. Columns with more than 300 trays and unreasonably large reflux ratios are required to separate relatively pure ethylbenzene as "overhead" (material accumulated at the top of the columns because of its low boiling point). For this reason, only a few refiners attempt to recover the ethylbenzene. Since p-xylene has a much higher melting point (+13°C) than the next highest C_8 aromatic compound (-25°C for o-xylene), it can be isolated by fractional crystallization in a purity that exceeds 99%. Figure 1-8 shows schematically a typical plant that will give good separation of the xylenes.

The relatively new Parex separation technique requires a bed of molecular sieves with pore sizes just large enough to admit the more linear p-xylene but not the other two "fatter" xylenes. The p-xylene can be adsorbed selectively into the pore structure and then desorbed in a hydrocarbon wash that can be separated easily from the p-xylene by distillation.

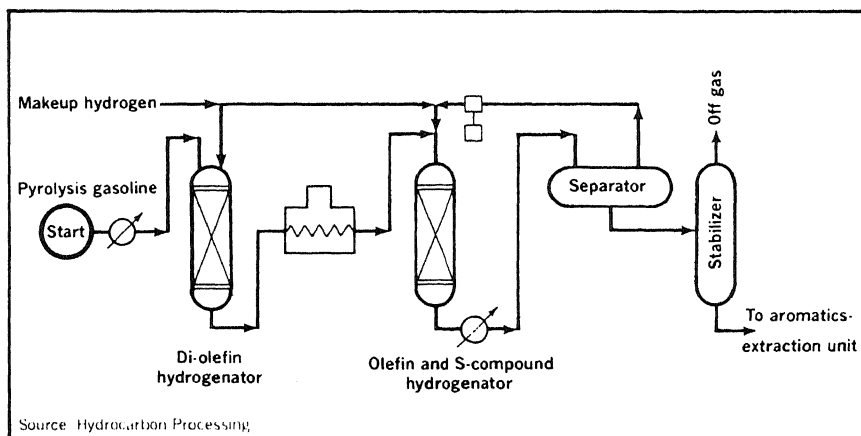


FIGURE 1-5. Scheme for two-stage hydrogenation plant for pyrolysis gasoline. From Brownstein, 1976.

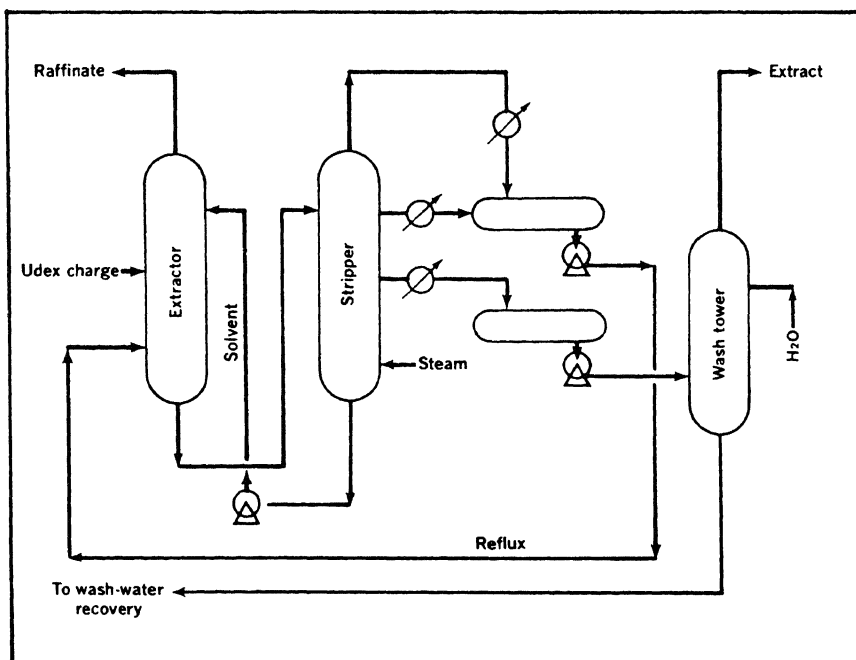


FIGURE 1-6. Udex process for extraction of aromatics. From Brownstein, 1976.

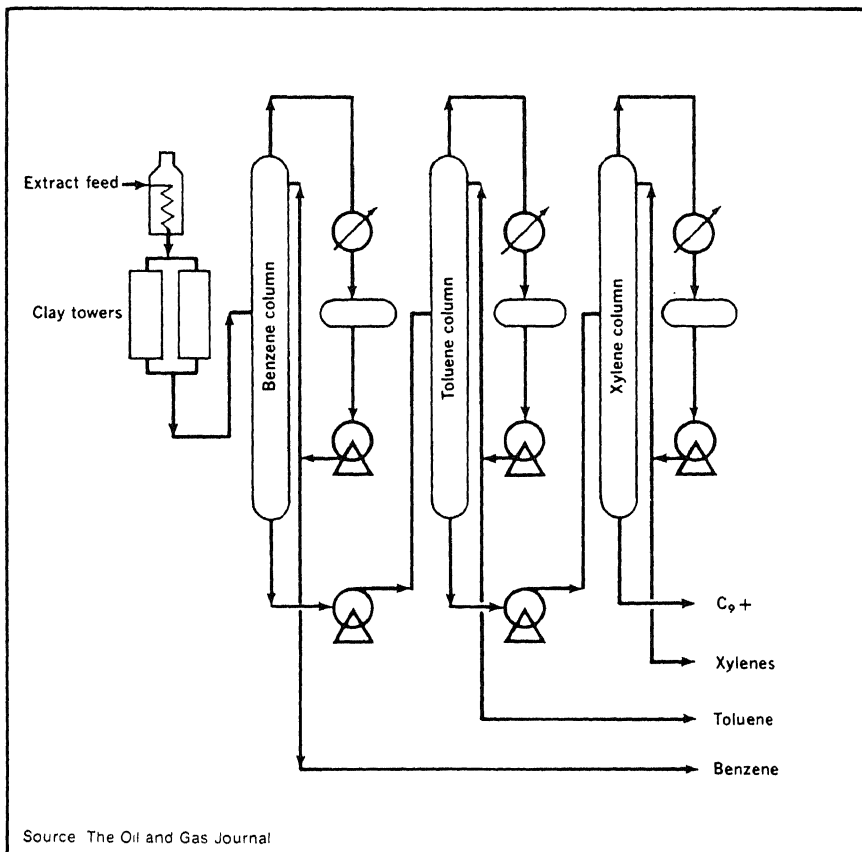


FIGURE 1-7. Scheme for fractionating aromatics with similar molecular weights. From Brownstein, 1976.

TABLE 1-11. Composition of Typical C₈ Aromatics Fraction in Catalytic Reformate^a

<u>Compound</u>	<u>Typical, %</u>	<u>Range, %</u>
<u>o</u> -Xylene	23	19-26
<u>m</u> -Xylene	40	35-40
<u>p</u> -Xylene	17	16-20
Ethylbenzene	20	17-21

^aFrom Brownstein, 1976.

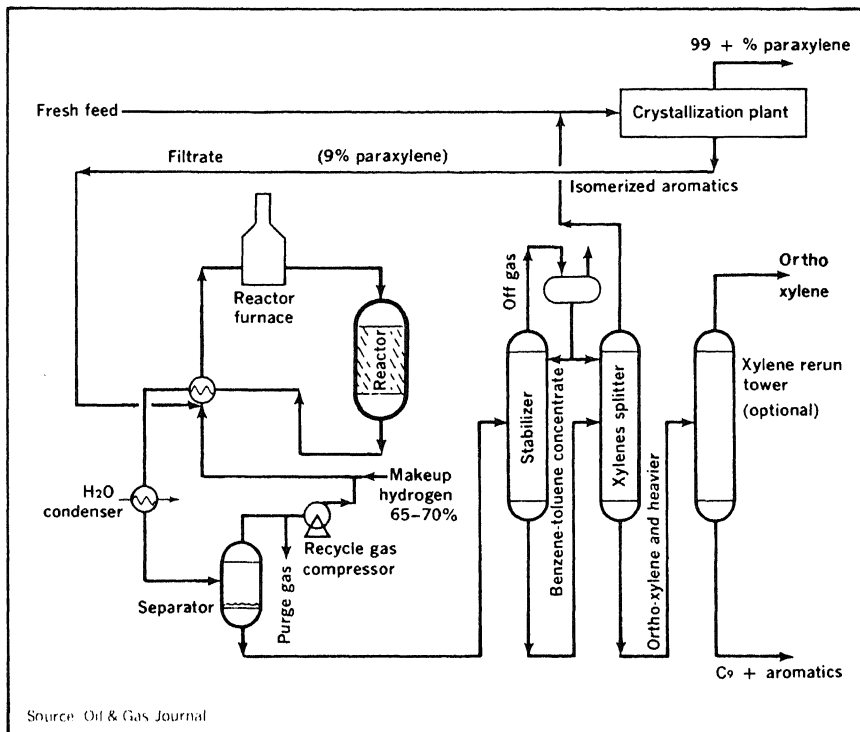
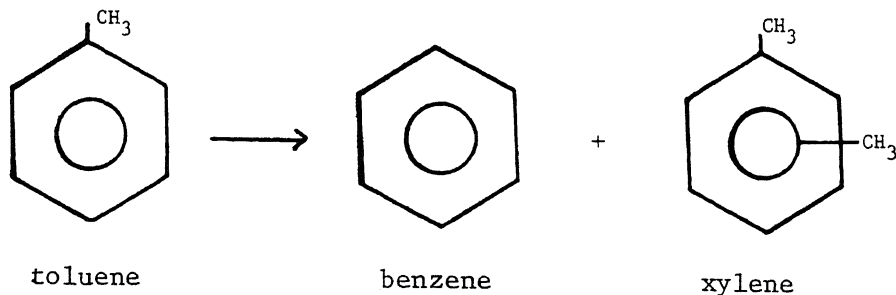
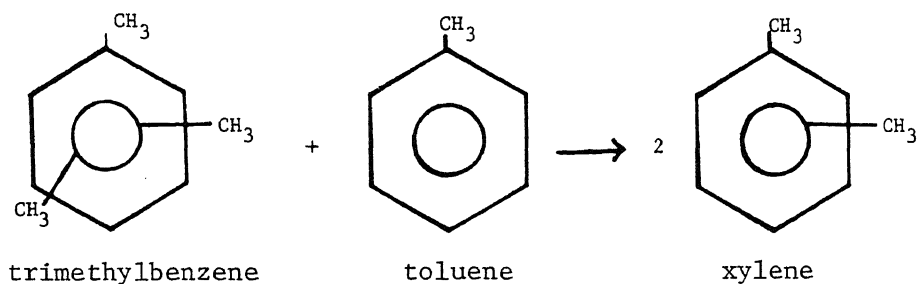


FIGURE 1-8. Scheme for processing xylenes. From Brownstein, 1976.

Another technique used to isolate m-xylene involves the selective formation of a complex that can be extracted from a mixture at room temperature. The complexing agent is a combination of hydrogen fluoride and boron trifluoride. After extraction, the complex is thermally decomposed, the m-xylene is recovered, and the agent is recycled to the xylene mixture.

Interconversion of Alkyl Benzenes

Processes called disproportionation or transalkylation are frequently used to interconvert the alkyl aromatics and to make benzene:



All of these are vapor phase catalytic processes that use non-noble transition metals. These processes have the advantage of producing o-, m-, and p-xylene (Table 1-12, Brownstein, 1976).

TABLE 1-12. Composition of C₈ Fraction in Typical Reformate versus Products from Transalkylation^a

<u>Compound</u>	<u>Reformate Xylenes</u>	<u>Disproportionation/ Transalkylation Xylenes</u>
<u>o</u> -Xylene	23	25
<u>m</u> -Xylene	40	50
<u>p</u> -Xylene	17	25
Ethylbenzene	20	--

^aFrom Brownstein, 1976.

The largest source of benzene is the hydrodealkylation (hydrocracking) of toluene or larger alkyl aromatics:

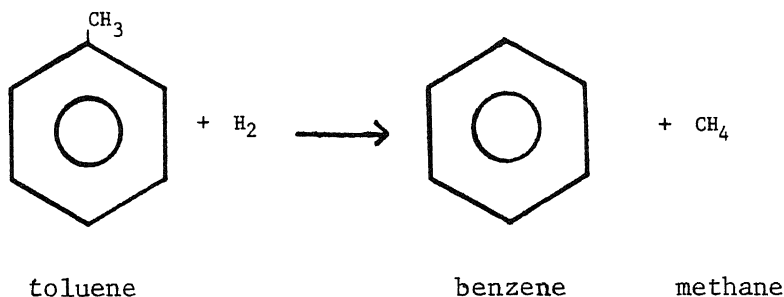
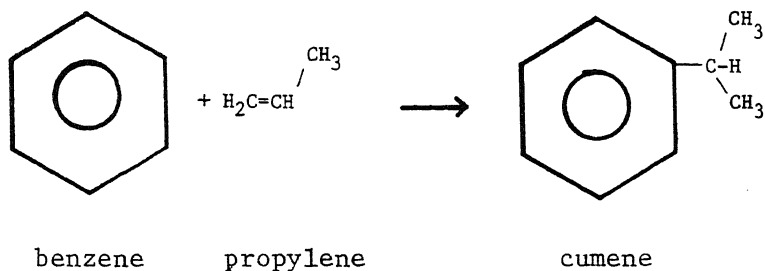


Figure 1-9 presents a schematic for a typical plant producing benzenes by this process.

Production of Cumene

Although some cumene (isopropylbenzene) occurs naturally in petroleum, it is also produced primarily for commercial use by alkylating benzene with propylene over a solid acidic catalyst:



A schematic diagram for a typical plant using a five-bed reactor, each filled with a phosphoric acid catalyst, is shown in Figure 1-10. An excess of benzene is fed to the reactors, and the unreacted benzene is separated and recycled. Based on the net benzene and propylene fed, the process yields more than 90% cumene. Essentially, cumene is used only as an intermediate chemical in the production of acetone and phenol.

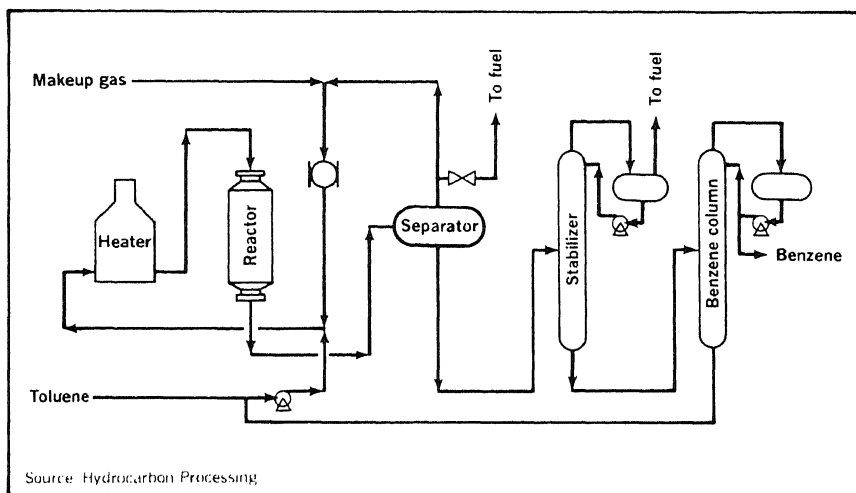


FIGURE 1-9. Schematic diagram for toluene hydrodealkylation plant.
From Brownstein, 1976.

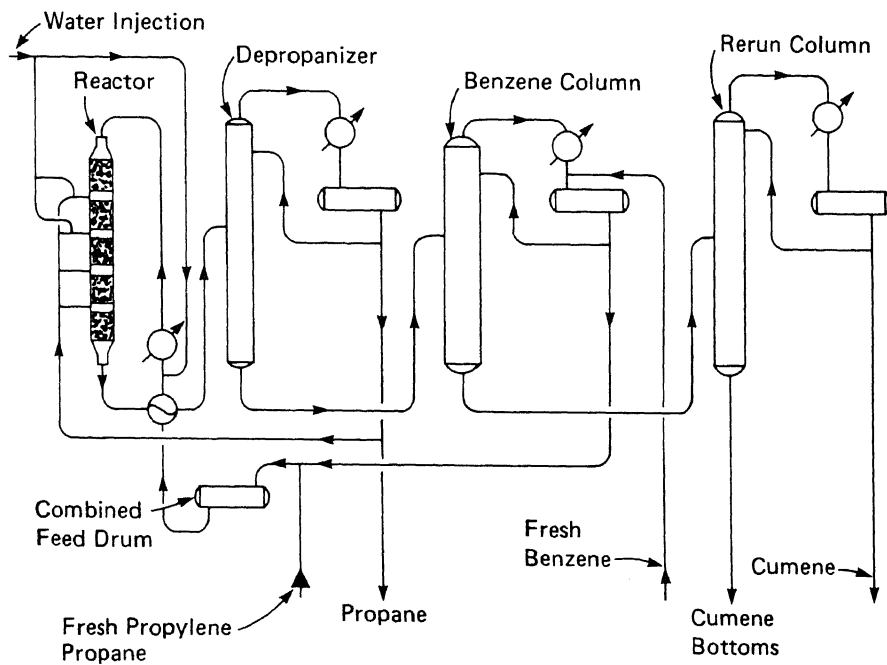


FIGURE 1-10. Solid phosphoric acid process for cumene production.
From Ward, 1965.

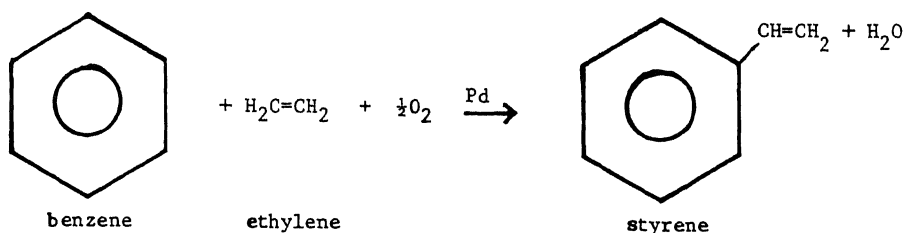
Production of Ethylbenzene

Although ethylbenzene occurs naturally and is also formed during petroleum reforming, it is not economical to isolate this compound from the catalytic raffinate because of the difficulties involved in separating it from the other C_8 aromatics. As with cumene, more than 90% of all the ethylbenzene used in the chemical industry is produced by alkylating benzene with ethylene via the Friedel-Crafts reaction with soluble aluminum chloride catalysts at temperatures between 100°C and 200°C (Figure 1-11). A solid zeolite is also an effective catalyst in this reaction, but at much higher temperatures and pressures. Although the yields of ethylbenzene are lower with the zeolite catalyst than with the aluminum chloride, the zeolite system avoids some of the problems associated with disposal of the reactive by-products that result from the use of aluminum chloride.

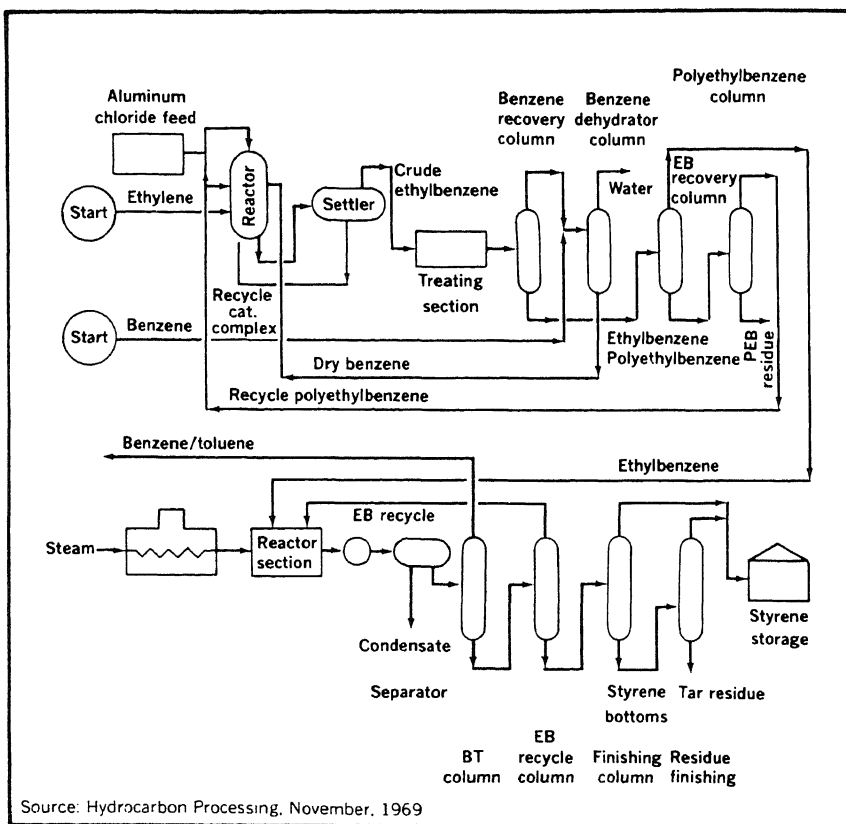
Production of Styrene

The only important use for purified ethylbenzene is in the manufacture of styrene, which is accomplished by catalytic dehydrogenation at high temperatures and at pressures below 1 atm. Steam supplies heat to the radial flow fixed-bed reactors for the endothermic reaction and prevents the formation of coke on the promoted iron oxide catalyst. Figure 1-11 shows an integrated flow scheme for the production of both the intermediate ethylbenzene and the final product, styrene.

Most of the recent work to develop alternative processes to produce styrene has involved oxidative coupling reactions. One study calls for the reaction of benzene and ethylene with molecular oxygen in the presence of a homogeneous palladium catalyst to form styrene and water in a single step:



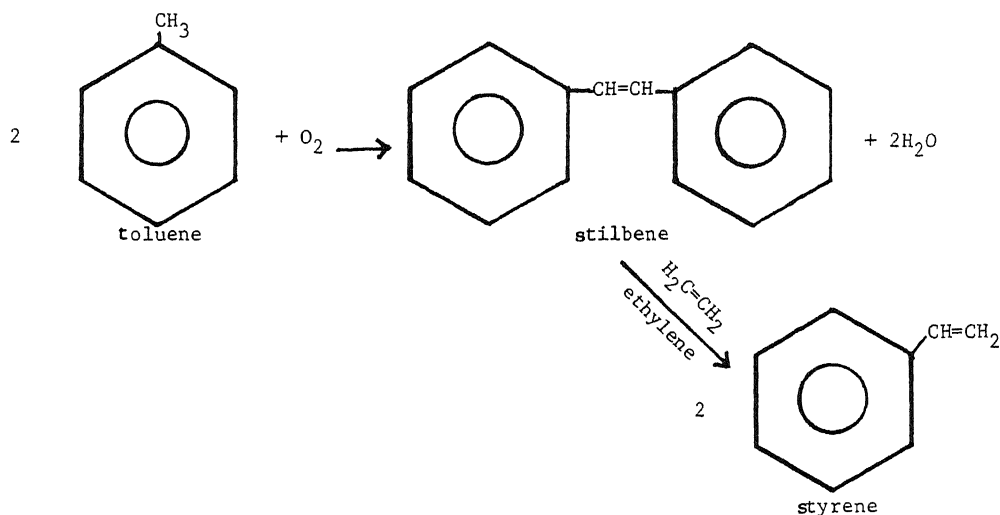
The added oxygen shifts the dehydrogenation equilibrium to the right by removing H_2 as H_2O .



Source: Hydrocarbon Processing, November, 1969

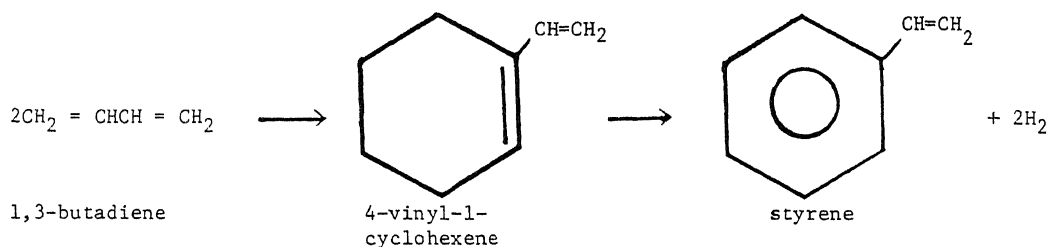
FIGURE 1-11. Scheme for an integrated plant to produce ethylbenzene and styrene. From Brownstein, 1976.

Another approach (Sherwin, 1979) is oxidative coupling of two toluene molecules to form stilbene, which can react with ethylene to form two molecules of styrene:



Unfortunately, this will almost certainly involve two reaction steps, which detract from its economic feasibility. Nonetheless, investigators have continued to explore this area since toluene is less expensive and more easily obtainable than benzene and two molecules of styrene are obtained for each molecule of ethylene reacted.

In a third approach (Sherwin, 1979) to the production of styrene, 1,3-butadiene is dimerized in a Diels-Alder reaction to form 4-vinyl-1-cyclohexene, which can easily be dehydrogenated over an appropriate catalyst such as iron oxide:



Finally, some recent studies have indicated that styrene can be formed very selectively by the oxidative dehydrogenation of ethylbenzene over a supported palladium catalyst promoted with fluorine (Fujimoto and Kunugi, 1979). Since this process is exothermic, it does not require a supply of steam to provide heat as in currently used processes.

Since none of these alternative processes is near commercial realization, most of the styrene produced in the United States during the next 20 years will probably come from modifications of present dehydrogenation technology.

Production of Styrene Oxide

Styrene oxide was prepared in 1905 by treating α -phenyl- β iodoethanol with potassium hydroxide (Fourneau and Tiffeneau, 1905). Now, it is produced commercially either by treatment of styrene chlorohydrin with concentrated potassium hydroxide or by epoxidation of styrene with peroxyacetic acid (Lapkin, 1965).

Commercial production of styrene oxide in the United States was first reported in 1974 (U.S. International Trade Commission, 1976). Annual production of the one U.S. producer is between 450 and 900 metric tons. In Japan, styrene oxide has been produced commercially since 1964. One company produced 1,800 metric tons in 1976 and exported 9.9 metric tons.

Styrene oxide has been detected as a by-product in commercial samples of styrene chlorohydrin (Dolgoplov and Lishcheta, 1971), as a volatile component in a tobacco concentrate (Demole and Berthet, 1972), and in effluent water from latex manufacturing plants in Louisville, Kentucky, and from chemical manufacturing plants in Louisville and in Memphis, Tennessee (Shackelford and Keith, 1976).

ALTERNATIVE PRODUCTION METHODS FOR ALKYL BENZENES

Fischer Tropsch Process Plus Reforming

The increasing cost and uncertainty of imported crude oil supplies has spurred intense efforts to develop domestic fuels from nonpetroleum sources, namely coal and shale. One process, which has been used extensively in South Africa under the name of Sasol, involves the conversion of coal into synthesis gas (CO and H_2). This gas can be turned into gaseous (via methanation) or liquid (via Fischer-Tropsch synthesis) hydrocarbons. The Fischer-Tropsch process yields primarily low octane, linear paraffins that

must be upgraded by severe reforming into usable fractions of gasoline (including aromatics). Although this process is known to work, the resultant gasoline cannot compete economically with that produced by refining processes based on petroleum.

Gasoline from Methanol

In another process, the synthesis gas from coal is converted into methanol or dimethylether. A selective ZSM-5 zeolite catalyst will convert these compounds directly into high octane gasoline that contains large fractions of aromatics. Table 1-13 shows the spectrum of compounds that can be produced by this process under relatively mild conditions, e.g., low temperature and low pressure. Note that the aromatics (mainly toluene and compounds with higher molecular weights) comprise more than one-third of the products formed. Undoubtedly, this type of process will be used much more frequently if we depend more heavily on coal as a basis for fuels and chemicals.

USES OF ALKYL BENZENES

As Mixtures

In Gasoline. As shown in Table 1-8, alkyl benzenes comprise an important portion of gasoline, ranging from 35% to 50% by weight in unleaded gasoline and averaging approximately 30% to 32% in regular and premium grades in Los Angeles (Mayrsohn *et al.*, 1978). Table 1-9 provides a more detailed listing of individual alkyl benzene compounds in a composite gasoline sample obtained in Los Angeles (Mayrsohn *et al.*, 1978). Various brands and grades of gasoline were weighted by their consumption in 1978 to arrive at these figures.

The percentage of alkyl benzenes in virgin gasoline is relatively low, approximately 10% (National Academy of Sciences, 1975). However, as discussed previously, this content is increased by catalytic reforming (Table 1-7), by blending in pyrolysis gasoline (a by-product of alkene production), or by the direct addition of individual alkyl benzenes.

In Solvents. Alkyl benzenes are used widely as solvents for paints, adhesives, and pesticides. This category of use is a potential major area for concern since the compounds are released directly into the atmosphere during application. In confined locations, such as in the home, relatively high atmospheric levels can occur, especially during painting.

In 1968, petroleum naphtha comprised approximately 60% of the total solvents used in the United States (National Academy of Sciences, 1975). This solvent, which is the lightest fraction distilled from petroleum, consists primarily of alkanes. Approxi-

TABLE 1-13. Synthesis of Gasoline from Methanol at 371°C with Different Reaction Pressures^a

Conditions and Percent Distribution	Reaction Pressure, atm			
	1.0	5.5	25	50
WHSV ^b	1.65	1.44	1.44	1.44
Conversion, %	99.9	99.2	99.3	98.0
Product distribution, mol %				
C ₁ -C ₄ aliphatics	40.94	28.84	26.40	25.44
C ₅ aliphatics	17.62	33.83	37.18	35.12
Benzene	NA ^c	0.96	0.87	0.79
Toluene	NA	4.69	2.50	1.46
C ₈ aromatics	NA	12.33	8.55	6.23
C ₉ aromatics	NA	12.25	12.06	11.98
C ₁₀ aromatics:	NA	7.10	12.44	18.86
Diethylbenzene	NA	1.20	1.04	0.95
Dimethylethylbenzene	NA	1.78	1.70	1.59
Durene	NA	3.77	9.31	15.58
Total aromatics	41.44	37.33	36.42	39.32
TOTAL all products	100.00	100.00	100.00	99.88

^aFrom Brownstein, 1976.

^bWeight hourly space velocity.

^cNot applicable.

mately 10% to 30% is composed of alkyl benzenes as a result of their natural occurrence in raw petroleum. Levy *et al.* (1971) reported limited data indicating that the aromatic content of six mineral spirits varied from 8% to 53%.

In addition to their presence in distillate solvents, relatively pure alkyl benzenes are also used widely as solvents. Table 1-14 lists data for the consumption of individual solvents in 1968 and 1978. The use of toluene and xylenes approximately doubled during this period. This parallels the increase in reforming capacity as shown in Figures 1-3 and 1-4.

Of course other compounds could be used to replace alkyl benzenes in their use as solvents. Among these are chloroform, benzene, and *n*-hexane. However, since each of these solvents is probably more hazardous than alkyl benzenes, it is likely that none of them are acceptable substitutes.

As Pure Substances

Toluene. A detailed breakdown of the uses of toluene in the United States during 1971 is shown in Figure 1-12. From these data Walker (1976) calculated that uses dispersing toluene into the atmosphere account for the consumption of 76% of the total production plus imports. Toluene is used predominantly as a component of gasoline (2.1×10^6 metric tons) and as a solvent (4.8×10^5 metric tons). Since 1971 preceded the production of catalyst-equipped motor vehicles, the amount of toluene used in motor vehicle fuel is probably considerably higher today.

These production figures apparently include neither toluene native to the petroleum from which gasoline is derived nor the toluene produced "in situ" in gasoline via catalytic reforming or production of pyrolysis gasoline by alkane cracking (Walker, 1976). Nor do they apparently include toluene present in distillate solvents such as petroleum naphtha.

In 1971, automobiles alone consumed 264.1×10^9 liters (approximately 2.7×10^8 metric tons) of gasoline (U.S. Bureau of the Census, 1979). If 7% of this amount consisted of toluene (Table 1-9), then 1.9×10^7 metric tons of toluene were consumed in automobiles instead of the lower amount implied in Figure 1-12, which shows a production figure of 2.1×10^6 metric tons for the toluene used in aviation and motor gasoline. The 7% estimate for toluene in gasoline underestimates the total use by ignoring gasoline used for aviation and diesel fuel used in trucks (103×10^9 liters).

TABLE 1-14. Use of Alkyl Benzenes as Solvents

Compound	Use, metric tons/year ^a		
	1968 ^b	1978 ^c	Year not reported ^d
Petroleum naphtha ^e	4,000,000	-- ^f	--
Toluene	220,000	400,000	320,000
Xylenes ^g	160,000	350,000	500,000
<u>o</u> -Xylene	--	<10,000	--
<u>p</u> -Xylene	--	< 4,500	--
Ethylbenzene	--	<37,000	--
Cumene	--	<15,000	--
Benzene	--	45,000	--

^aData rounded off from original sources.

^bMSA Research Corp., 1972.

^cSuta, 1979.

^dLee et al., 1979.

^eApproximately 20% of this product is probably composed of alkyl benzenes. This source rate for C₇ and C₈ alkyl benzenes probably exceeds that of the pure solvents.

^fData not available.

^gIncludes ethylbenzene and xylene isomers.

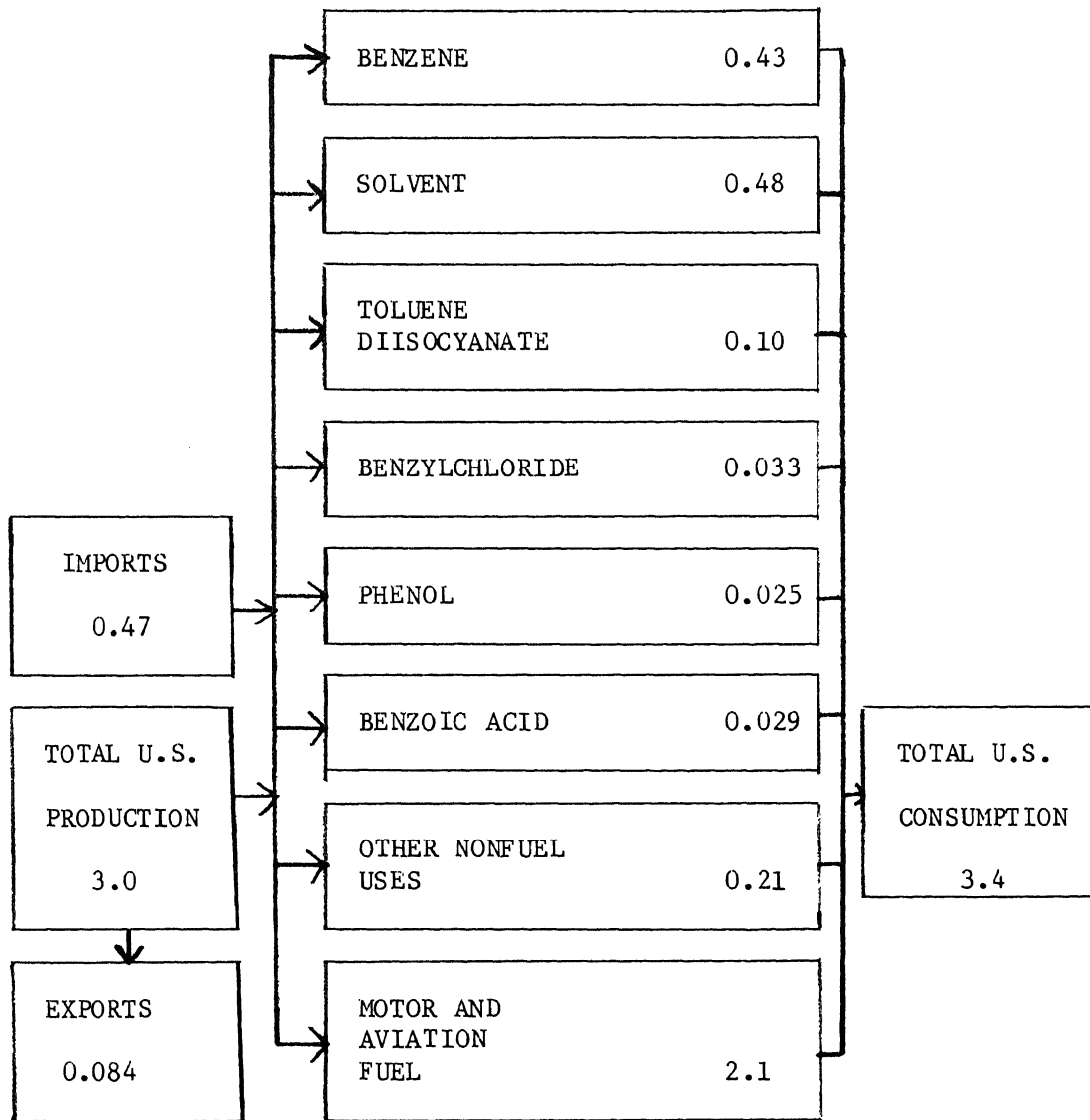


FIGURE 1-12. Flow of toluene in the United States during 1971. Quantities in million metric tons. These figures include only toluene labelled as "produced." It excludes most of the toluene present in gasoline and mixed solvents. Adapted from Walker, 1976.

Thus, toluene listed as "produced" for use in gasoline accounts for only approximately 10% of the actual toluene consumed in gasoline (Figure 1-4).

Xylenes. Xylenes are constituents of a wide variety of consumer products (U.S. Environmental Protection Agency, 1978b). They are used in the manufacture of phthalic anhydride, isophthalic acid, and terephthalic acid for the paint and fiber industries and in the production of xylidenes, which are antiknock ingredients in motor fuels. Either commercial or other blends of xylenes are used as industrial, cleaning, degreasing, processing, extracting, or thinning solvents (Cier, 1970). The mixed xylenes are used as diluents in the paint industry, in agricultural sprays for insecticides, and in gasoline blends.

Ethylbenzene. Significant quantities of ethylbenzene are present in mixed xylenes. Among other uses, these mixtures are constituents of gasoline blends. In the plastic and rubber industries, ethylbenzene is used as an initial substrate reactant in the production of styrene (Paul and Soder, 1979). Most of the plants in this industry are located in Texas and Louisiana. Of the approximately 3.8 million metric tons of ethylbenzene produced annually in the United States, more than 90% is used in the manufacture of styrenes (U.S. International Trade Commission, 1980).

Cumene. Cumene is used principally in the manufacture of phenol and acetone, to a lesser extent as a component of motor fuels, particularly aviation fuel, and, according to patent literature, as a catalyst for acrylic- and polyester-type resins. It is also used widely as a diluent or thinner for paints and enamels, as a solvent, and in organic synthesis. During World War II, cumene occupied a particularly important place as a component of the aviation fuel and helped measurably in increasing the 100-octane gasoline supplies during this period (McAllister, 1955). The proportion of cumene currently used as a blending component in fuels for internal combustion engines is difficult to estimate because manufacturers customarily do not disclose this information. For typical base stocks, cumene is said to be capable of replacing from 2.5 to 3 times its volume of isobutane-butylene alkylate. Cumene hydroperoxide is quite useful as a chain initiator in polymer chemistry.

Styrene. Although styrene was originally used principally in the manufacture of synthetic styrene-butadiene rubber (SBR), styrene plastics are now the major outlet for the monomer. These products, including polystyrene, rubber-modified polystyrene, styrene-butadiene copolymer, styrene-acrylonitrile copolymer (SAN), and acrylonitrile-butadiene-styrene terpolymer (ABS), rank third in volume in the plastics field behind polyethylene and polyvinyl chloride. Styrene

homopolymer accounts for approximately 25% of the monomer production and is widely used in packaging, toys, housewares, appliances, etc. It is a clear, inexpensive plastic that can be molded easily or extruded into practically any shape or form. Expanded foams of polystyrene have excellent heat-insulating and flotation properties. They are used in construction, refrigeration, and packaging (International Agency for Research on Cancer, 1979).

Since polystyrene breaks more easily upon impact than many other plastics, a number of copolymers have been formulated to provide increased shock resistance. Rubber-modified polystyrene, which is generally referred to as "impact polystyrene," is not transparent like the homopolymer but is much more durable. It is manufactured either by blending an SBR with polystyrene, by dissolving rubber in the monomer and polymerizing, or by polymerizing styrene in the presence of small granules of the rubber. The latter technique is known as graft polymerization. The styrene content of this product generally ranges from 88% to 97%. It is used in appliances, luggage, and other products that require increased breakage resistance (International Agency for Research on Cancer, 1979).

ABS polymers, which serve much the same purpose as impact polystyrene, are becoming increasingly popular. They are used widely in motor vehicles, e.g., in instrument panels, and in refrigerator interiors and telephone housings. SAN plastics provide excellent chemical resistance and clarity and are receptive to an almost unlimited number of dyes. The resins generally contain between 70% and 75% styrene and are harder and more rigid than conventional polystyrene. Styrene-butadiene copolymer contains more than 50% styrene, as compared to synthetic SBR which is made from the same ingredients but contains only about 20% styrene. This copolymer is a latex material used as an emulsion in the manufacture of paint and surface coatings for cloth and paper. Chemically modified copolymers of styrene-divinylbenzene form the basis of many ion-exchange resins (International Agency for Research on Cancer, 1979).

Polystyrene is one of the most widely produced thermoplastics, and it is used for many different purposes (Tossavainen, 1978). The very low monomer and other solvents (e.g., ethylbenzene) containing polystyrenes are useful in the packaging of food. When additional lubricants, such as mineral oil, butyl stearate, etc., are added to polystyrene, easy-flow materials are produced. Stiff-flow polystyrene has a high molecular weight and low volatility and is useful for extrusion applications.

Speciality polystyrenes are made mostly of pure polystyrene. Their molecular structures and/or additives are adjusted to make them useful in special applications.

Acrylonitrile, butadiene, α -methylstyrene, methylmethacrylate, and maleic anhydride have been copolymerized with styrene to yield commercially significant copolymers (Holden and Milkovich, 1967; Moacanin et al., 1969; Molau, 1965; Simpson, 1966; Vanzo, 1966; Ziembra, 1964; Zimmerman and O'Connor, 1967).

Graft copolymers utilizing styrene are reported in numerous publications and are summarized in several textbooks (Battaerd and Tregear, 1967; Burlant and Hoffman, 1960; Ceresa, 1962). Many grafting systems have been studied including the grafting of styrene or styrene-acrylonitrile onto butadiene elastomers, which form the basis of high-impact styrene polymers. Polyethylene, cellulose, and polyvinylchloride are examples of other substrate polymers for styrene grafting (Harmer, 1967).

Approximately 87% of the styrene consumed in the United States during 1976 was used in the production of plastics and resins: polystyrene resins, 61%; ABS and SAN resins, 11%; styrene-butadiene copolymer resins, 8%; and unsaturated polyesters, 7%. Approximately 11% was used to make SBR, and the remaining 2% was used in miscellaneous applications. Styrene is also used to make saturated polyester resins reinforced with glass fiber, which are used primarily in construction materials and boats, to synthesize styrene-divinylbenzene copolymers, which are used as a matrix for ion-exchange resins, and to produce styrenated oils and styrene oxide (International Agency for Research on Cancer, 1979).

In Western Europe, 71% of the styrene used in 1974 was accounted for by plastics and resins (polystyrene resins, 63%; ABS and SAN resins, 8%). Eleven percent was used in the production of SBR lattices, and the remaining 18% was used in miscellaneous applications, e.g., ethylene-propylene copolymers. Worldwide, an estimated 62% of the styrene produced in 1974 was used in the manufacture of polystyrene (including expandable polystyrene); 13% in ABS and SAN resins; 17% in SBR; and 8% in other applications.

The U.S. Food and Drug Administration (FDA) permits the use of styrene as a synthetic flavoring substance and adjuvant, as a cross-linking agent in polyester resins, and in rubber articles (5 wt % max) that are intended for use in contact with food. Styrene copolymers with acrylic or methacrylic monomers may be used in semirigid acrylic- and vinyl-chloride-based plastics. Some of them, e.g., those with maleic anhydride, may be used in paper and paperboard coatings that are intended for use in contact with food. Other styrene copolymers permitted in products that come into contact with food include styrene-divinylbenzene cross-linked resins, styrene-maleic anhydride copolymers, and styrene-methyl methacrylate copolymers

used in plastics. The amounts present may not exceed those reasonably required to produce the intended effect (U.S. Food and Drug Administration, 1977).

Styrene Oxide. Styrene oxide is used as a reactive diluent in epoxy resins to reduce the viscosity of mixed systems prior to curing (Lee and Neville, 1967). It is also used as an intermediate in the preparation of agricultural and biological chemicals, cosmetics, surface coatings, and in the treatment of textiles and fibers. In Japan, styrene oxide is used as a raw material for the production of phenylstearyl alcohol, which is used in perfume (International Agency for Research on Cancer, 1979).

The FDA has ruled that styrene oxide may be used as a catalyst and cross-linking agent for epoxy resins in coatings for containers with a capacity of 3,785 liters or more when such containers are intended for repeated use in contact with beverages containing up to 8% alcohol by volume (U.S. Food and Drug Administration, 1977).

Styrene oxide has also been used to produce resinous condensation products that have been used for the manufacture of varnishes with excellent water resistance (Lapkin, 1965).

SOURCES OF ALKYL BENZENE EMISSIONS

Point Sources Versus Mobile Sources

The release of pollutants into the atmosphere is traditionally broken down into stationary, or point, sources and mobile, or non-point, sources. Point sources for alkyl benzenes include oil spills, gasoline refining or reforming, storing and transferring of fuel, chemical manufacturing that either produces these compounds or uses them as feedstocks, coke production, the use of paints, adhesives, pesticides, or industrial solvents for cleaning, and a variety of other applications. Nonpoint sources are customarily related to transportation. These include gasoline emissions from automobiles, diesel emissions from trucks, trains, and ships, and emissions from aviation fuel. Of these sources, gasoline-powered vehicles contribute the bulk of the emissions. Other widely dispersed sources are gasoline service stations, home use of solvents, and cigarette smoking.

Emissions from Solvents

Since all solvents for home use and most of those for industrial use are destined to evaporate into the atmosphere, most usage probably results in emission.

Sexton and Westberg (1980) have recently determined the concentrations of hydrocarbons in the solvent plume from a large automobile assembly plant. They reported that 82% of this atmospheric plume was composed of alkyl benzenes and that only 18% was composed of alkanes. Toluene comprised more than 50% of the total weight of the 25 individual hydrocarbons identified. A detailed breakdown of the alkyl benzene content of the plume is given in Chapter 4 in Table 4-4. The plume concentrations were proportional to the rates at which the compounds were used in the plant: toluene, 396 liters/hr; xylene, ~132 liters/hr; naphtha, ~161.5 liters/hr; mineral spirits, ~37.6 liters/hr; and "aromatic hydrocarbons," ~158 liters/hr. Assuming complete agreement between usage at the source and ambient plume measurements, one may calculate that in addition to the alkyl benzenes, which comprise 78% of the listed usage, 20% of the total of naphtha and mineral spirits contained alkyl benzenes as well in order for 82% of the ambient plume to consist of alkyl derivatives of benzene. This 20% figure corroborates the estimates made in Table 1-14.

Although Table 1-14 indicates substantial growth in the use of alkyl benzenes as solvents between 1968 and 1978, Suta (1979) has reported a decline in the demand for these products since 1975 and has predicted that 1980 figures will show a continuing decline. This is attributed to the high photochemical reactivity of these solvents in photochemical smog (see Chapter 4). In 1967, Los Angeles County established "Rule 66" to limit the reactivity of solvents. This rule combined with others elsewhere in the country was claimed by Suta to have affected the demand for aromatic solvents adversely. However, this projection is certainly not borne out by the automotive plant emissions reported by Sexton and Westberg (1980).

Emissions from the Use of Automotive Fuel

Emissions from the evaporation and combustion of gasoline are an important source of alkyl benzenes in the environment. As conversion to catalyst-equipped automobiles progresses, the quantity of compounds in gasoline increases.

Components of gasoline can enter the atmosphere via a variety of different pathways. Empty storage tanks are generally saturated with gasoline vapors. If the air is not recovered, filtered, or trapped when the tank is filled, all of these vapors are transferred to the atmosphere. Vapors are released from various tanks during filling operations at several stages prior to final consumption, e.g., from the tank in the consumer's automobile, from the gas station tank, from the tank truck, from the storage tank, etc. Alkyl benzenes in gasoline tend to have high boiling points. Con-

sequently, their concentrations in these vapors are generally less than those in bulk gasoline. In recent years, transfer losses have come under increasing control, particularly in bulk gasoline facilities.

Simple spillage when customers' tanks are overfilled also contributes to evaporative losses. Older model cars lose vapors by "breathing" in response to variations in temperature. The vapors are lost both from the tank and from the carburetor. Newer models, i.e., those manufactured after 1971, are equipped with vapor recovery systems that are estimated to reduce these emissions by approximately 30% (U.S. Environmental Protection Agency, 1977b).

Hydrocarbons, including alkyl benzenes, are present in automobile exhaust. They result both from incomplete combustion of gasoline in the cylinder and from cracking or reforming of the original gasoline molecules. The composition of gasoline is reflected in the composition of exhaust, but considerable modification occurs as well. For instance, Doelling et al. (1971) and Wigg et al. (1972) determined that the alkyl benzene content of exhaust is proportional to that in fuel, whereas Dishart (1970) reported that the concentrations of alkyl benzenes with low molecular weights increased by cracking of higher molecular weight members of this class.

Since 1968, the hydrocarbons emitted in the exhaust of new automobiles have been reduced by approximately 90% (U.S. Environmental Protection Agency, 1978a). The most recent reductions are due to the installation of catalysts in most new cars in the United States. A historical review and future projections of total hydrocarbon emissions are presented in Table 1-15.

The need for unleaded fuel stems from the installation of catalytic converters on cars to decrease the emission of harmful pollutants in the exhaust. These devices contain platinum, palladium, and/or rhodium as the active ingredients. All of these catalytic materials are readily deactivated or "poisoned" by lead and will not remain active if the lead content of the fuel exceeds approximately 0.05 g of lead per gallon (approximately 13.2 mg/liter). Lead can be either a permanent or a temporary poison for these catalysts depending on the temperature of the converter, the concentration of lead in the exhaust, and the duration of exposure. Occasional exposure to leaded gasoline, e.g., to one tankful of leaded gasoline in 10, will not permanently poison the catalyst.

The data shown in Figure 1-13 are typical indications of this effect. These data were obtained in tests conducted on the emissions from a new car, which was owned by the City of Houston (H. C. McKee, personal communication, 1980). Hydrocarbon emissions from

TABLE 1-15. Estimated Emissions of Hydrocarbons from Automobiles and Other Mobile Pollution Sources in the United States, 1955-1985^a

Source	Estimated hydrocarbon emission, million tons/year						
	1955	1960	1965	1970	Projected Estimates		
					1975	1980	1985
Automobiles	9.9	12.0	13.0	11.0	5.9	2.4	0.9
Trucks and buses	1.2	1.4	1.7	1.9	1.7	1.4	1.4
Aircraft	0.3	0.3	0.2	0.3	0.2	0.1	0.1
Off-highway	0.7	0.7	0.7	0.6	0.6	0.6	0.5
TOTAL	12.1	14.4	15.6	13.8	8.4	4.5	2.9

^aTable from National Academy of Sciences, 1976. Data derived from National Petroleum Council, 1971. Types of tons not specified.

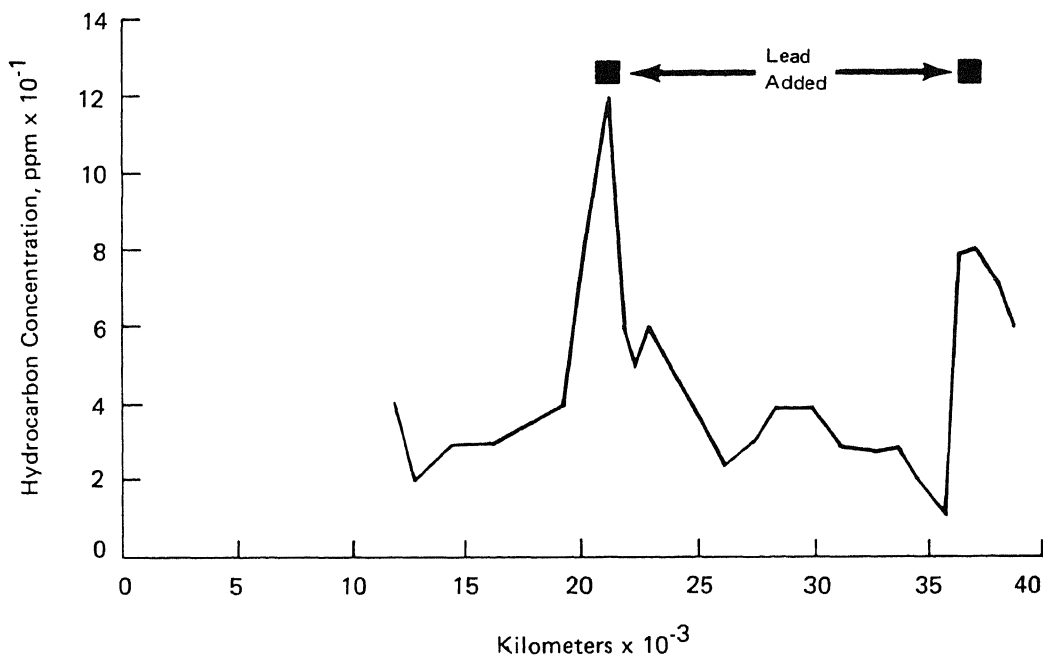


FIGURE 1-13. Effect of leaded gasoline on emissions of hydrocarbons from an automobile with a catalytic converter. Data from Herbert C. McKee, City of Houston, personal communication, 1980.

the exhaust of this automobile, which was equipped with an oxidizing catalytic converter, were carefully monitored under idle conditions. During the first 19,400 km, only unleaded fuel was used, and the hydrocarbon emissions averaged approximately 40 ppm in the tail pipe. At that time, the tank was filled with 14 gallons (~ 53.2 liters) of leaded fuel containing 2.04 g/gal (~ 0.54 g/liter), or 28.6 g of lead total. The hydrocarbon emissions increased to a range of 90-120 ppm. However, as soon as the unleaded fuel was used again, the emissions decreased to values similar to those obtained originally. At 34,000 km the tank was filled 3 times in succession with 40 gallons (~ 152 liters) of leaded gasoline containing 0.83 g/gal (~ 0.22 g/liter), or 33.2 g lead total. Again the emissions of hydrocarbons increased, but this time not to as high a value as that observed when the higher concentration of lead was used. The new spark plugs installed shortly before the leaded fuel was added the second time may have caused the hydrocarbon emissions from the engine to be somewhat lower in this case. Nevertheless, it is clear that lead decreases the effectiveness of the catalytic converters, but that the effect is reversible provided that the exposure to lead is not too frequent. Additional information concerning catalytic converters can be found in a review article by Hightower (1976).

Catalysts significantly modify the composition of hydrocarbons in automobile exhaust since they show greater activity for unsaturated hydrocarbons. The U.S. Environmental Protection Agency (1978a) has published a typical distribution of these compounds in the exhaust of automobiles with and without catalysts:

	<u>Alkyl benzenes</u>	<u>Alkanes</u>	<u>Alkenes</u>	<u>Alkynes</u>
With catalyst:	17%	62%	18%	3%
Without catalyst:	24%	40%	26%	11%

These percentages apply to new automobiles and may change as the catalyst in the car ages and drops in efficiency. Other data are provided in a report of the National Academy of Sciences (1974). For example, concentrations in exhaust measured before and after the use of a platinum catalyst supported in the exhaust line by a monolithic, honeycomb-shaped structure show clearly that the catalyst is more effective in removing aromatics (86% of the toluene) and olefins (86% of the isobutene) than it is for removing paraffins (64% of the isopentane and none of the methane) (Table 1-16). Since methane is not considered to be a significant pollutant, its contribution to the photochemical activity is zero. On the other hand, stronger pollutants such as alkyl aromatics and olefins, whose activity

Effect of Oxidation Catalyst on Hydrocarbon Emissions from
Automobile Exhausts^a

Concentration, ppm		<u>Percent Reduction</u>	<u>HEW Activity</u>		<u>Percent Reduction</u>
<u>Before</u>	<u>After</u>		<u>Before</u>	<u>After</u>	
45	45	0	0	0	0
14	5	64	14	5	64
22	3	86	153	21	86
59	8	86	177	24	86
536	136	75	1,768	265	85

tional Academy of Sciences, 1974.

indices are considerably greater than unity, are more effectively removed in the converters. Thus, although the hydrocarbons were decreased by only 75%, the HEW photochemical activity was reduced by 85%. The catalytic converters are most effective in removing those compounds that are the most reactive in the environment.

The composition of gasoline, gasoline vapor, and auto exhaust has been determined by Mayrsohn et al. (1977) who studied sources of atmospheric hydrocarbons in Los Angeles during 1974. Some of the results for alkyl benzenes are listed in Table 1-17. The relative amounts of the primary components of the alkyl benzenes are similar in exhaust and in raw gasoline, but contribute less to the vapors. These investigators reported that alkyl benzenes comprised 45% of the exhaust. This is significantly higher than the 24% reported by the U.S. Environmental Protection Agency (1978a) and may represent a difference in the composition of fuel. Mayrsohn et al. estimated that auto exhaust accounted for 53% and gasoline 22% of total atmospheric nonmethane hydrocarbons in Los Angeles in 1973. The remainder of the atmospheric hydrocarbons was attributed to commercial and geogenic natural gas, which do not contribute appreciable amounts of alkyl benzenes. In this study solvents were not considered as a source. These results may no longer be applicable because of the increased use of catalysts in automobiles. The data in Table 1-17 were obtained from automobiles without catalysts, which were in use at the time of the study.

Because of the constant changes in the types and numbers of motor vehicles, the increasing quantity of catalysts in use, and the aging of catalysts now in service, it is difficult to estimate reliably the source strengths of transportation-related alkyl benzenes. Current estimates indicate that evaporative emissions from automobiles manufactured in 1975 and later are greater than their exhaust emissions (U.S. Environmental Protection Agency, 1977b). National transportation-related emissions for 1974 were estimated to be 11.3×10^6 metric tons and for 1975 (preliminary), 10.6×10^6 metric tons (U.S. Environmental Protection Agency, 1977b).

Assuming, conservatively, that alkyl benzenes comprise 15% of emissions from exhaust, evaporation, and spillage, the emissions from this source would be approximately 1.5×10^6 metric tons per year.

If we estimate that approximately 20% of the total emissions of alkyl benzenes from motor vehicles are due to toluene (Table 1-17), the emission rate would be 3×10^5 metric tons per year. Using the measured exhaust toluene emission rate of 0.0396 g/km (Black and High, 1977) and scaling the evaporative emissions to the benzene estimates of the U.S. Environmental Protection Agency (1977a), Suta (1979) estimated annual toluene emissions for 1976. He attributed

TABLE 1-17. Alkyl Benzenes in Transportation-Related Emissions During 1974 in Los Angeles^a

Compound	Weight percent		
	Auto Exhaust	Gasoline (Spillage)	Gasoline Vapor (Gasoline Transfer)
Benzene	3.0	2.4	1.1
Toluene	8.8	9.7	2.1
<u>m</u> - and <u>p</u> -Xylene	9.1	9.9	2.2
<u>o</u> -Xylene	3.4	3.6	0.4
Propylbenzene	0.4	0.3	-
3-Ethyltoluene	6.6	6.5	0.5
1,2,4-Trimethylbenzene	4.8	3.8	0.3
1,2,3-Trimethylbenzene	1.2	1.4	0.1
Dimethylethylbenzene	0.7	2.7	0.1
Butylbenzene	2.1	1.7	-
TOTAL	40.1	42.0	6.8
Toluene as % of total alkyl benzenes	22	23	31

^aFrom Mayrsohn et al., 1977. These authors estimated that exhaust hydrocarbons contributed 53% and gasoline spillage and evaporation 22% of total nonmethane hydrocarbons in Los Angeles during 1974. Reprinted with permission from Atmos. Environ. Copyright 1977 Pergamon Press, Ltd.

9×10^4 metric tons per year to exhaust and 1.3×10^5 to evaporation. The total of 2.2×10^5 compares favorably with the estimate of 3×10^5 , which is based on total hydrocarbon emissions from mobile sources.

Gasoline is probably responsible for most of the current transportation-related emissions of alkyl benzenes to the atmosphere. The various grades of diesel fuel, kerosene, etc., typically contain between 15% and 25% alkyl benzenes (Table 1-7), but the volume used is less than that of gasoline. Moreover, the emissions of hydrocarbons from diesel engines are less than those from spark ignition engines. The U.S. Environmental Protection Agency (1977b) has estimated that diesel-powered vehicles contribute approximately 5% of the total hydrocarbons emitted by gasoline vehicles. However, there is a trend for these types of emissions to increase in relative importance. Projections indicate that they will actually surpass emissions from automobiles by 1985 (Table 1-15).

Oil Spills

Alkyl benzenes may also be emitted to the atmosphere via evaporation from oil spills, including routine tanker discharge and leakage, minor accidents, discarded lubricants, etc., as well as from major catastrophic spills. Alkyl benzenes account for approximately 10%-25% of crude oil (National Academy of Sciences, 1975). They may also be released from spills of Bunker C or No. 6 fuel oils, diesel or No. 2 fuel oils, and light petroleum products such as kerosene or gasoline. A very rough breakdown is presented in Table 1-18. Crude oils and distillates obtained from them vary widely in their composition, depending upon their geographic origin. Other sources of alkyl benzenes in rivers, lakes, and oceans are gasoline spillage from boats, industrial effluents, municipal waste treatment facilities, landfills, and agricultural runoff.

The lower molecular weight alkyl benzenes would be expected to evaporate rapidly either from true solutions or from saturated two-phase systems. Mackay and Leinonen (1975) have estimated the evaporation rate of several compounds from a saturated 1-m deep solution at 25°C. Toluene, xylene, and ethylbenzene were estimated to have half-lives of 5 to 6 hr in solution. Evaporation directly from an oil spill is also rapid for C_2 to C_{10} hydrocarbons. Several investigators have found no hydrocarbons in this group a few hours following surface oil spills (Butler, 1975; Harrison et al., 1975; McAuliffe, 1977; Smith and MacIntyre, 1971).

TABLE 1-18. Approximate Composition of Major Petroleum-Derived Fuels^a

Fuel	Composition, %		
	Alkyl Benzenes	Alkanes	Nitrogen-Sulfur Oxygen
Crude oil	15 ^b	80	5
No. 6 fuel oil (Bunker C)	25	60	15
No. 2 fuel oil	25	75	NA ^c
Kerosene	15	85	NA
Virgin gasoline	10	90	NA
Blended gasoline	25	75	NA

^aNational Academy of Sciences, 1975.

^bTable 1-4 implies that the alkyl benzene content of crude oil is lower.

^cData not available.

Conversely, unpolluted bodies of water are potential sinks for the ppb levels of atmospheric alkyl benzenes that are normally present in the vicinity of anthropogenic emission sources. This subject is discussed more fully in Chapter 4.

The U.S. Coast Guard has estimated that 2.8×10^4 metric tons of oil were spilled into U.S. water during 1971 (National Academy of Sciences, 1975). If 15% were alkyl benzenes, then 4.2×10^3 metric tons were involved. Of these, 7.2% were on inland water and 86% coastal. Since toluene averages approximately 0.5% of crude oil (Brownstein, 1976; Table 1-4), the source rate for this chemical was approximately 140 metric tons per year.

From Manufacturing Sites

Some alkyl benzenes are emitted into the environment at the site where they are produced. The exact amounts of these emissions either are not known or are classified as proprietary information and carefully withheld by the producers. However, an attempt was made in 1978 to estimate the emissions at each location (primarily petroleum refineries) in which these materials were produced. Detailed information is listed by site in Tables 1-19 and 1-20 for toluene only (Mara *et al.*, 1979). Approximately 0.003% of the toluene produced is estimated to be lost to the environment at the production sites. Other alkyl benzenes show similar trends: fractions lost range from 0.003% to a high of approximately 0.15% for styrene and ethylbenzene (Mara *et al.*, 1979).

Additional amounts of the alkyl benzenes are lost during transportation of the compounds, but these amounts are rather small. Another, perhaps significant source of environmental pollution is provided by gasoline vending stations. The amount provided by this source is estimated to be approximately the same as that lost at the production sites (Suta, 1979).

Miscellaneous Sources

Table 1-21 presents estimated nationwide emissions during 1974 for sources of hydrocarbons other than those described above. The alkyl benzenes contained in these hydrocarbon emissions are poorly characterized, but are unlikely to be very high. Individually, these sources are small compared to transportation-related hydrocarbons (11.3×10^6 metric tons/year), but in the aggregate they comprise approximately 30% of this source.

TABLE 1-19. Location of U.S. Producers and Their Estimated Production of Toluene in 1978^a

Company and Location	1978		Raw Material
	Capacity, 10 ³ metric tons	Estimated Production, 10 ³ metric tons	
Amerada Hess Corp. St. Croix, V.I.	460	370	Catalytic reformate
American Petrofina, Inc. Beaumont, Tex.	120	100	Catalytic reformate
Big Spring, Tex.	160	130	Catalytic reformate
Ashland Oil, Inc. Ashland, Tex.	100	80	Catalytic reformate
	30	30	Coke-oven light oil
N. Tonawanda, N.Y.	40	30	Catalytic reformate
	10	10	Coke-oven light oil
Atlantic Richfield Channelview, Tex.	140	110	Pyrolysis gasoline
Houston, Tex.	120	100	Catalytic reformate
Wilmington, Calif.	50	40	Catalytic reformate
Bethlehem Steel Sparrows Point, Md.	<3	<3	Coke-oven light oil
CF&I Steel Corp. Pueblo, Colo.	Negligible	Negligible	Coke-oven light oil
The Charter Company Houston, Tex.	50	40	Catalytic reformate
Coastal States Gas			

<u>Company and Location</u>	1978		<u>Raw Material</u>
	<u>Capacity, 10³ metric tons</u>	<u>Estimated Prd₃duction, 10³ metric tons</u>	
Commonwealth Oil Refining Co., Inc. Ponce, P.R.	390 50	320 40	Catalytic reformat Pyrolysis gasoline
Crown Central Petroleum Corp. Pasadena, Tex.	50	40	Catalytic reformat
Dow Chemical, USA Freeport, Tex.	13	10	Catalytic reformat
Exxon Corp. Baytown, Tex.	410	332	Catalytic reformat
Getty Oil Company El Dorado, Ks.	13	10	Catalytic reformat
Gulf Oil Corp. Alliance, La. Philadelphia, Pa. Port Arthur, Tex.	210 90 50 70	170 80 40 50	Catalytic reformat Catalytic reformat Catalytic reformat Pyrolysis gasoline
Kerr-McGee Corp. Corpus Christi, Tex.	150	120	Catalytic reformat
LTV Corporation Aliquippa, Pa.	7	7	Coke-oven light oil
Marathon Oil Co. Tampa, Fla.			

Company and Location	1978		Raw Material
	Capacity, 10 ³ metric tons	Estimated Production, 10 ³ metric tons	
Mobil Corporation Beaumont, Tex.	280 16	220 13	Catalytic reformat Pyrolysis gasoline
Monsanto Co. Chocolate Bayou, Tex.	30 130	30 110	Catalytic reformat Pyrolysis gasoline
Phillips Petroleum Company Sweeny, Tex. Guayama, P.R.	30 340	30 270	Catalytic reformat Catalytic reformat
Quintana-Howell Joint Venture Corpus Christi, Tex.	60	50	Catalytic reformat
Shell Chemical Co. Deer Park, Tex.	200	160	Catalytic reformat
Sun Company Corpus Christi, Tex. Marcus Hook, Pa. Toledo, Ohio Tulsa, Okla.	140 150 250 70	110 120 200 50	Catalytic reformat Catalytic reformat Catalytic reformat Catalytic reformat
Tenneco, Inc. Chalmette, La.	100	80	Catalytic reformat
Texaco, Inc. Port Arthur, Tex. Westville, N.J.	90 130	80 110	Catalytic reformat Catalytic reformat
Union Carbide Corp.			

TABLE 1-19 (Continued)

Company and Location	1978		Raw Material
	Capacity, 10 ³ metric tons	Estimated Production, 10 ³ metric tons	
Union Oil Company of California Lemont, Ill.	60	50	Catalytic reformat
Union Pacific Corp. Corpus Christi, Tex.	100	80	Catalytic reformat
United States Steel Clairton, Pa.	30	20	Coke-oven light oil
Geneva, Utah	3	3	Coke-oven light oil
TOTAL	5,192	4,205	

^aFrom Mara et al., 1979. Production data derived based on data from U.S. International Trade Commission, 1979.

Exxon Corp. Baytown, Tex.	13	12
Getty Oil Company El Dorado, Ks.	4	Negligible
Gulf Oil Corp. Alliance, La.	5	6
Philadelpia, Pa.	4	3
Port Arthur, Tex.	1	3
Kerr-McGee Corp. Corpus Christi, Tex.	4	4
LTV Corporation Aliquippa, Pa.	1	Negligible
Marathon Oil Company Texas City, Tex.	Negligible	2
Mobil Corporation Beaumont, Tex.	Negligible	8
Monsanto Company Chocolate Bayou, Tex.	1	5
Phillips Petroleum Company Sweeny, Tex.	2	1
Guayama, P.R.		9
Quintana-Howell Joint Venture Corpus Christi, Tex.	13	2
Shell Chemical Company Deer Park, Tex.	1	6
Sun Company		

<u>Company and Location</u>	<u>Estimated Emissions, metric tons</u>	<u>Company and Location</u>	<u>Estimated Emissions metric tons</u>
Sun Company (Continued)			
Toledo, Ohio	7	Union Carbide Corp.	
Tulsa, Okla.	2	Taft, La.	2
Tenneco, Inc.		Union Oil Company of California	
Chalmette, La.	3	Lemont, Ill.	2
Texaco, Inc.		Union Pacific Corp.	
Port Arthur, Tex.	3	Corpus Christi, Tex.	3
Westville, N.J.	4	Union States Steel	
		Clairton, Pa.	1
		Geneva, Utah	Negligible
		TOTAL	149

^aFrom Mara et al., 1979.

TABLE 1-21. Miscellaneous Sources of Emissions of Hydrocarbons
in the United States During 1974^a

<u>Source</u>	<u>Emissions, million metric tons/year</u>
Stationary fuel combustion	1.3
Solid waste	0.8
Forest fires	0.7
Agricultural burning	0.1
Coal refuse burning	0.1
Structural fires	<0.1
TOTAL	3.0

^aU.S. Environmental Protection Agency, 1977b.

Coke Production. Walker (1976) estimated that 0.24 kg of toluene is emitted per metric ton of coke produced in a plant with no emission controls and that this yields a total annual emission of 14,000 metric tons of toluene in the United States. These appear to be very high estimates. Although 14,000 metric tons is negligible nationally, these emissions could have some local impact since they are produced in relatively limited areas of the country.

Drinking Water. Toluene has been detected in the drinking water of several U.S. cities in concentrations ranging from trace to as high as 19 $\mu\text{g/liter}$ (Suta, 1979). Normal concentrations are less than 1 $\mu\text{g/liter}$. Toluene has also been measured in municipal effluents in concentrations from 1 to 150 $\mu\text{g/liter}$ (U.S. Environmental Protection Agency, 1978b). These concentrations compare with its solubility of $534.8 \pm 4.9 \text{ mg/liter}$ (Sutton and Calder, 1975). However, the driving force for loss from water to the atmosphere is the partition coefficient or Henry's Law coefficient for equilibrium between the atmosphere and solution. The value for toluene is 6.1 atm liter/mol. Since typical ambient concentrations of toluene in polluted urban areas are approximately 10^{-8} atm, the solution phase concentration of toluene at equilibrium would be 0.14 ng/liter. Thus, polluted bodies of water serve as a source for atmospheric toluene and other alkyl benzenes. This subject is discussed further in Chapter 4.

Cigarette Smoking. A seldom considered source is cigarette smoking. Alkyl benzenes have been quantitatively determined in smoke (Grob, 1965; Johnstone et al., 1962). The data indicate a probable total yield of 0.5 mg/cigarette. Combined with the figures indicating that 670 billion cigarettes were produced in 1977 (U.S. Bureau of the Census, 1977), these data indicate a national yearly emission of 335 metric tons, which is of no national significance (however, see Localized Exposure, below).

Vegetation. Vegetation is a significant source of volatile hydrocarbons, chiefly terpenes. Using the estimate of Rasmussen and Went (1965), the U.S. Environmental Protection Agency (1978a) estimated that the annual U.S. emission rate is approximately 20 million metric tons. It is unlikely that a significant fraction of this amount (which is subject to considerable uncertainty) could be attributable to alkyl benzene compounds. Nevertheless, alkyl benzenes are minor constituents of emissions from plants. Indeed, toluene is named for the tropical tolu tree, which produces the compound naturally. Toluene and other alkyl benzenes have been identified in roasted filberts (Kinlin et al., 1972), in peanuts and macadamia nuts (Crain and Tang, 1975; Walradt et al., 1971), in grape essence (Stevens et al., 1967), and in cooked potatoes (Nursten and Sheen, 1974).

There is no evidence that significant amounts of alkyl benzenes are produced naturally in the United States, either in urban or rural atmospheres.

LOCALIZED EXPOSURE

Apparently, there are no data on concentrations of nonoccupational, localized exposure. The general public is probably exposed to higher than ambient levels of alkyl benzenes while having their automobile tanks filled with gasoline or while using gasoline as a solvent. Alkyl benzenes are also constituents of common solvents for paints and other coatings, for adhesives, and for some pesticides. Tobacco smoke provides yet another localized source.

Continual exposure would be experienced by people living near gasoline stations or chemical facilities in which alkyl benzenes are used. Suta (1979) has estimated that people living near production plants are exposed to concentrations between 0.1 to 0.2 ppb. These levels are insignificant compared to average urban levels that are attributable largely to automobiles and solvents.

Exposure of the general public to individual chemical solvents has been reviewed by Lee et al. (1979), who found that ethylbenzene and mixed xylenes provided the highest exposures of all solvents. These compounds along with toluene are widely used as solvents for paints and allied products. Mineral spirits, paint thinner, petroleum naphtha, gasoline used as a solvent, etc., which were not considered by Lee et al., contain significant but variable amounts of alkyl benzenes, typically between 10% and 50%. Moreover, the relatively greater use of such mixed solvents by the public (Table 1-14) indicates that ignoring these solvents is a mistake when in fact they may dominate the exposure of the general public.

Exposure concentrations will be highest for the low molecular weight and hence more volatile alkyl benzenes. Actual levels achieved will depend upon evaporation rate and ventilation. Although less volatile compounds will evaporate more slowly, dosages for equal amounts of two different compounds may be the same in the home if it is occupied during and after painting. Consumer exposure to these compounds will be greatest during painting, but such exposures and concentrations resulting from painting are hard to characterize and have apparently not been studied.

Suta (1979) suggested that data on occupational exposure might provide a basis for estimating exposure of the general public. In light of this, he reviewed some data on occupational exposure. For example, during the painting of a ship hold, the concentration of toluene was 32ppm and xylenes were reported to be 229 ppm. In other occupational situations toluene levels ranged from 0.1 to 60 ppm. A high of 685 ppm toluene was measured near the fountain

The alkyl benzenes in cigarette smoke were measured by Johnstone et al. (1962) and Grob (1965) (Table 1-22). Apparently, most of these compounds occur only in the smoke and not in the tobacco itself. Assuming very roughly that the smoke from a single cigarette has a volume of 10 liters, then approximately 100 μg of toluene₃ per cigarette would have a concentration of approximately $10^4 \mu\text{g}/\text{m}^3$, or about 3 ppm in the smoke. Thus, smokers will be exposed to average concentrations of alkyl benzenes significantly higher than urban exposure levels of approximately 10 ppb. Furthermore, "smoke-filled rooms" should have an alkyl benzene content in excess of ambient air in cities. Although there are insufficient data for making a quantitative assessment, an approximation for "passive smoking" may be made. Carbon monoxide averages 17 mg per cigarette, and measured concentrations of carbon monoxide in enclosed smoking areas generally run from 10 to 100 ppm (U.S. Department of Health, Education, and Welfare, 1979). If toluene averages 0.1 mg per cigarette, this would yield a range of 0.06 to 0.6 ppm in smoking areas. These levels are considerably higher than background urban levels in most cases. The actual situation is complicated by relative mainstream versus sidestream concentrations. These factors should be studied before any firm conclusions are drawn.

Exposure to very high levels of alkyl benzenes also occurs during glue sniffing. Those levels would be proportional to vapor pressures of the individual compounds. Vapor pressure of toluene is approximately 28 torr, and the C₈ aromatics have vapor pressures of approximately 8 torr. These very high levels correspond to about 40,000 and 10,000 ppm, respectively.

PRESENT CONTROL TECHNOLOGY

The major potential sources of environmental contamination by alkyl benzenes are their uses in transportation-related fuels and as solvents. Controls must therefore have an impact on these uses in order to be effective.

Current techniques will minimize the emissions from manufacturing sites, i.e., from petroleum refineries and chemical plants. However, it is difficult to ensure that these techniques are used consistently. Defective processing equipment should be replaced, leaks repaired, and effective contingency plans perfected for dealing with spills in the plants. Present emissions of these compounds from plants are estimated to range from 30 to 150 ppm of the hydrocarbons processed.

The installation of catalytic converters on automobiles has already greatly decreased emissions of all hydrocarbons, particularly alkyl benzenes and olefins, from exhaust systems. As the older cars

TABLE 1-22. Alkyl Benzene Content of Cigarette Smoke

Compound	Average Yield from Cigarettes in Several Countries, μg ^a			
	United Kingdom ^b	USSR ^b	Argentina ^b	NR ^{c,d}
Benzene	27	48	12	32
Toluene	46	164	65	80
Ethylbenzene	7	20	7	<14
<u>m</u> -Xylene	30	48	20	1.6
<u>o</u> -Xylene	22	48	20	< 6
Styrene	NR ^e	NR	NR	10
Mesitylene	9	11	8	1
Cumene	11	14	7	NR

^aTypical cigarette weight is 1 gram.^bJohnstone *et al.*, 1962.^cGrob, 1965.^dCountry not reported.^eNot reported.

with converters are continually removed due to attrition from the vehicle pool, the emissions of hydrocarbons from this source are almost certain to continue decreasing. Assuming that there are 10 million cars produced annually at an additional cost of \$200 each for the catalytic converters, one can estimate that this type of control costs approximately \$2 billion per year (National Academy of Sciences, 1973). Further reduction of emissions from this source may be impractical from an engineering viewpoint.

Other major sources of motor vehicle emissions are evaporation of spilled gasoline and loss of vapors during fuel transfer. The former can be reduced by educating the public, and the latter is already controlled in many areas of the country by vapor recovery systems. Once the automobile is made as clean as possible, the next step is a reduction in vehicle miles traveled. Many areas of the country are currently considering various methods to achieve this, including increased capacity and use of mass transit, car and van pooling, etc.

Another area in which present controls appear to be inadequate is solvent use. For example, the concentrations could be quite high in drycleaning establishments and paint shops. Adequate ventilation should be encouraged, and solvent recovery systems should be installed in places where large quantities of solvents are vented. The cost-effectiveness of alternative control measures needs to be studied.

Diesel-powered vehicles also contribute emissions of alkyl benzenes and other hydrocarbons to the environment. Although the control of hydrocarbons from these sources has not had high priority in the past, it might receive greater attention in the future as its proportionate use increases.

ECONOMIC BENEFITS OF CONTROLLING ALKYL BENZENE EMISSIONS

There is no geographical area of any appreciable size in which ambient atmospheric concentrations of alkyl benzenes are known to be harmful to plant or animal life. However, as reactive hydrocarbons, they can contribute to the formation of photochemical oxidants that are known to be harmful to life and property. At present, the extent of this contribution and the manner in which it varies in response to changes in various atmospheric factors and emissions from natural, industrial, and transportation sources are ill-defined.

Any sound economic assessment of the net benefits to be derived from controlling alkyl benzene emissions clearly requires an understanding of this contribution. Without such an assessment, economic analysis is restricted to setting bounds within which the benefits and costs of control must fall. If existing ambient concentrations of alkyl benzenes by themselves are harmless, the lower bound of the

net benefits of such control must be negative since control of alkyl benzene emissions would be costly. Alternatively, if higher-than-background levels of photochemical oxidants were to disappear in the absence of ambient alkyl benzenes, then all the harm usually attributed to oxidants could be removed by controlling alkyl benzenes. The upper bound of net benefits would then be the emission level that maximizes the difference between the money equivalent of photochemical oxidant damage reductions and alkyl benzene controls.

The costs of preventing emissions of alkyl benzenes are obviously relevant to decisions to control these emissions. The information presented below on the benefits of controlling photochemical oxidants would be unquestionably relevant to these same decisions if and when the contribution of alkyl benzenes to ambient photochemical oxidants is finally understood. However, even without this knowledge, this information has relevance for decisionmakers. In particular, to the extent the contributions of various reactive hydrocarbons to oxidant formation are undifferentiated in the decisionmaking process, the severity of alkyl benzene controls will be related directly to the benefits decisionmakers believe can be achieved by reducing ambient oxidants. If the perceived benefits of controlling ambient oxidants are few, alkyl benzene emissions are unlikely to be scrutinized carefully. If they are many, these emissions might be sharply reduced even though exact quantitative information on how they aid in the formation and duration of ambient oxidants is lacking.

Perhaps the most complete economic studies of the benefits of reducing ambient concentrations of oxidants are those sponsored by the U.S. Environmental Protection Agency to examine the South Coast Air Basin of southern California (Adams et al., 1980; Brookshire et al., 1979; Thayer and Schulze, 1980). In its draft air quality management plan, the Southern California Association of Governments and South Coast Air Quality Management District, Los Angeles (1979) calculated that achievement of the 1979 ambient oxidant standards would require basin-wide reductions of 874.8 metric tons per day in reactive hydrocarbon emissions along with 441 metric tons per day in nitrogen oxide emissions.

To estimate the urban benefits of this reduction, Brookshire et al. (1979) selected six pairs of neighborhoods. Each pair was similar in all respects except air pollution. Applying hedonic reasoning (Rosen, 1974) to 1978 data on 719 individual residential property sales in the six neighborhood pairs, they estimated the differences among residential property values that were attributable to air pollution. With a 9.25% discount rate, their results indicated that the annualized market value of the representative residential property would have been increased by \$312 to \$756 for a 30% improvement in 1978 annual average air pollution. The mean increase was \$504.

Recognizing that there is considerable controversy (e.g., Maler, 1977) concerning conditions under which property value differences can be used to infer willingness to pay for environmental improvements, Brookshire et al. (1979) also conducted a bidding game interview survey in the same six neighborhood pairs. In their study, neighborhood residents were presented with color photographs showing varying air qualities at well-known Los Angeles sites and asked whether they would be willing to pay increasingly higher prices for the depicted improvements in air quality. To ensure uniformity of perceptions among respondents, the investigators specified the requested payments carefully and described in detail the quantity, quality, location, institutional, and time dimensions of the depicted scenes. The mean household annual bid was \$348, a figure consistent with that obtained from the property value study. The authors ascribed about one-half of the annual bid to respondent-perceived aesthetic (visibility) benefits of the air quality improvement. The other half was assigned to respondent-perceived health benefits.¹

While accounting for the influence of property location and personal income on willingness to pay, Thayer and Schulze (1980) have extrapolated the results of Brookshire et al. (1979) to the entire South Coast Air Basin. They calculated that the urban benefits accrued as a result of conforming to the 1979 air quality standards amounted to between \$1.6 billion and \$3 billion in the basin.

The benefits that an improvement in air quality would provide for commercial agriculture in southern California can be added to the urban benefits described above. Using a price-endogenous quadratic programming model, Adams et al. (1980) have examined the economic impact of ambient oxidants upon production of 12 annual vegetable and two annual field crops in that region. They took into account the different tolerances of the yields of these crops to oxidant exposures, changes in input and output prices, and farmers' consequent decisions to undertake input and output substitutions and changes in location. In response to changing ambient oxidant levels, major adjustments in cropping patterns and locations were predicted and observed. Despite these farmers' attempts to ameliorate air pollution effects, there was an estimated 3% decline in the sum of producer rents and consumer surpluses. Producer rents comprised three-quarters of this percentage. Total 1976 benefits of achieving the 1979 ambient standards for the 14 crops would have been \$56

¹Bidding games, or other interview techniques, have traditionally been mistrusted in economics as a means of acquiring information on willingness to pay. However, see Brookshire and Crocker (1981) for a theoretical and practical defense of the bidding game technique.

million in 1979 dollars. Taking into account yield tolerances to oxidant air pollution, but neglecting all price and locational changes, a naive extrapolation by these authors of the 14 crop results to all southern California commercial agriculture implied 1976 oxidant control benefits of more than \$250 million (in 1979 dollars).

The preceding empirical results imply that the annual economic benefits of attaining the 1979 oxidant air quality standards in southern California probably range from \$1.85 billion to \$3.25 billion. No one knows what portion of these benefits might be captured by reducing the region's alkyl benzene emissions. At a minimum, this knowledge requires understanding of the part that alkyl benzenes play in the formation and duration of oxidants.

SUMMARY AND CONCLUSIONS

The alkyl benzenes are widely used as solvents in paint, adhesives, cleaning preparations, and pesticides, as major components of fuel for motor vehicles and airplanes and, to a lesser extent, diesel fuels, and as intermediaries in the manufacture of chemicals. Styrene is used mainly for the manufacture of polymers in the plastics and rubber industry.

The alkyl benzenes can be emitted into the atmosphere from a number of sources. Gasoline and solvents greatly outweigh any other source. This is reflected in Table 1-23, which lists estimated emissions for toluene, the most prevalent alkyl benzene in the atmosphere. As more and more automobiles come under emission control, it is likely that solvents will claim a larger proportion of the total. Considerations such as these--when applied to hydrocarbon emissions in general--have recently led the State of California to curtail the use of paints based on hydrocarbon solvents. The chief purpose is to meet the Federal Air Quality Standard for ozone, which is formed photochemically by the reaction of hydrocarbons and oxides of nitrogen. However, in the attempt to control ozone, atmospheric alkyl benzenes will decline as well.

Although it is common practice to weigh the potential environmental importance of a hydrocarbon on both its toxicity and on U.S. production figures, such as those in Table 1-1, the latter basis for judgment is open to question. It is clear that production figures do not include the majority of the hydrocarbons that are present in fuels, mixed solvents, and crude oil. The tendency of regulatory agencies to separate industrial from transportation sources contributes to this error. The bulk of the environmental emissions and exposure of the general public to alkyl benzenes are due to gasoline and solvents, particularly mixed solvents. This fact

TABLE 1-23. Emissions of Toluene to the Atmosphere, Metric Tons/Yr

Source	1971 ^a	1971 ^b	1977 ^c	1976 ^d	1977 ^e
Commercial production, storage, and trans- port	30,000				
Commercial usage	520,000				
Oil spills		140			
Coke production	14,000				
Solvent evaporation			320,000	400,000	
Cigarette smoking					80
Gasoline distribution:					
Auto tank filling			6,800		
Terminal loading and storage			51		
Service station tanks			200		
Gasoline-powered motor vehicle exhaust	1,300,000			90,000	
Evaporative emissions	300,000			130,000	

^aFrom Walker, 1976. These estimates are extremely conservative and are probably too large.

^bFrom National Academy of Sciences, 1975. Toluene calculated as 0.5% of total spilled oils.

^cFrom Eimutis and Quill, 1977.

^dFrom Suta, 1979.

^eBased on data of Johnstone et al. (1962) and U.S. Bureau of the Census (1977).

^fFrom Mara et al., 1979.

would not be apparent from studies of chemical production inventories. A further major source, diesel fuel usage, cannot be quantified because of insufficient data.

In a nonoccupational setting, individual exposure to alkyl benzenes is highest for cigarette smokers. So-called "passive smoking" would probably rank as the second highest exposure in terms of concentration. For urban dwellers this exposure would of course simply be added to the ambient alkyl benzene exposure caused by outdoor emissions from transportation, solvents, and other sources. It is not expected that alkyl benzenes would be removed significantly from air as it moves indoors. Exposure via passive smoking would depend upon the extent of indoor ventilation. Indoor pollution is likely to become more pervasive as buildings are made airtight in attempts to conserve energy. The use of solvent-based paints and stains in the home can lead to very high concentrations on a short-term basis, but actual levels are expected to be extremely variable. Apparently, there are no significant data on this subject.

REFERENCES

- Adams, R. M., T. D. Crocker, and N. Thanavibulchai. 1980. An Economic Assessment of Air Pollution Damages to Selected Annual Crops in Southern California. U.S. Environmental Protection Agency, Washington, D.C. 27 pp.
- Battaerd, H. A. J., and G. W. Tregear. 1967. Graft Copolymers. Interscience, New York. 551 pp.
- Black, F., and L. High. 1977. Automotive Hydrocarbon Emission Patterns in the Measurement of Nonmethane Hydrocarbon Emission Rates. Technical Paper 770144. Society of Automotive Engineers, Warrendale, Penna. 16 pp.
- Brookshire, D. S., and T. D. Crocker. 1981. The advantages of contingent valuation methods for benefit-cost analysis. Public Choice 36(2):235-252.
- Brookshire, D. S., R. C. d'Arge, W. D. Schulze, and M. Thayer. 1979. Methods for Valuing Aesthetics and Health Effects in the South Coast Air Basin: An Overview. Paper presented at the 72nd Annual Meeting of the Air Pollution Control Association, June 24-28, 1979, Cincinnati, Ohio. 27 pp.
- Brownstein, A. M. 1976. Trends in Petrochemical Technology: The Impact of the Energy Crisis. Petroleum Publishing Co., Tulsa, Oklahoma. 275 pp.
- Burlant, W. J., and A. S. Hoffman. 1960. Block and Graft Polymers. Reinhold, New York. 166 pp.
- Butler, J. N. 1975. Evaporative weathering of petroleum residues. The age of Pelagic tar. Mar. Chem. 3:9-21.
- Ceresa, R. J. 1962. Block and Graft Copolymers. Butterworth, Washington, D.C. 196 pp.
- Cier, H. E. 1970. Xylenes and ethylbenzene. Pp. 467-507 in H. F. Mark, J. J. McKetta, Jr., and D. F. Othmer, eds. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd edition, Volume 22. Interscience, New York.
- Crain, W. O., Jr., and C. S. Tang. 1975. Volatile components of roasted macadamia nuts. J. Food Sci. 40:207-208.

- Demole, E., and D. Berthet. 1972. A chemical study of Burley tobacco flavour (Nicotiana tabacum L.). I. Volatile to medium-volatile constituents (b.p. $\leq 84^{\circ}/0.001$ Torr). *Helv. Chim. Acta* 55:1866-1882.
- Dishart, K. T. 1970. Exhaust hydrocarbon composition. Its relation to gasoline composition. *Proc. Am. Pet. Inst., Div. Refin.* 50:514-540.
- Doelling, R. P., A. F. Gerber, and M. P. Walsh. 1971. Effect of gasoline characteristics on automotive exhaust emissions. Pp. 20-32, and discussion pp. 33-35, in *Effect of Automotive Emission Requirements on Gasoline Characteristics*. ASTM Special Publication 487. American Society for Testing and Materials, Philadelphia, Penna.
- Dolgoplov, V. D., and L. I. Lishcheta. 1971. Qualitative determination of by-products in commercial samples of styrene chlorohydrin. *Khim. Farm. Zh.* 5(11):55-56. [Chem. Abs. 76:27967b, 1972].
- Eimutis, E. C., and R. P. Quill. 1977. Source Assessment: Non-criteria Pollutant Emissions. Report No. EPA-600/2-77-107e. (Available from National Technical Information Service, Springfield, Va., as PB-270 550.) Industrial Environmental Research Laboratory, Research Triangle Park, N.C. 116 pp.
- Fourneau and Tiffeneau [no initials given]. 1905. Sur quelques oxydes d'éthylène aromatiques monosubstitués. *C. R. Acad. Sci.* 140:1595-1597.
- Fujimoto, K., and T. Kunugi. 1979. Oxidative dehydrogenation of ethylbenzene over modified palladium catalysts. *Prepr. Div. Pet. Chem., Am. Chem. Soc.* 24(1):310-317.
- Grob, K. 1965. Gas chromatography of cigarette smoke. Part III. Separation of the overlap region of gas and particulate phase by capillary columns. *J. Gas Chromatogr.* 3:52-56.
- Harmer, D. E. 1967. Reaction rates and physical properties in the radiation graft-copolymer system: Poly(vinyl chloride)-styrene. Pp. 203-213 in R. F. Gould, ed. *Irradiation of Polymers*. American Chemical Society, *Advances in Chemistry Series No. 66*. American Chemical Society, Washington, D.C.
- Harrison, W., M. A. Winnik, P. T. Y. Koong, and D. Mackay. 1975. Crude oil spills: Disappearance of aromatic and aliphatic components from small sea surface slicks. *Environ. Sci. Technol.* 9:231-234.

- Hightower, J. W. 1976. Catalysts for automobile emission control. Pp. 615-635, discussion p. 636, in B. Delmon, P. A. Jacobs, and G. Poncelet, eds. Preparation of Catalysts: Scientific Bases for the Preparation of Heterogeneous Catalysts. Proceedings of the International Symposium held at the Solvay Research Centre, Brussels, October 14-17, 1975. Elsevier Scientific Publishing Co., Amsterdam, The Netherlands.
- Holden, G., and R. Milkovich. 1967. Conjugated diene elastomers modified with block copolymers. U.S. Patent 3,322,856. Shell Oil Co. [Chem. Abs. 67:33637z, 1967.]
- International Agency for Research on Cancer. 1979. Styrene, polystyrene and styrene-butadiene copolymers. Pp. 231-274 in IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 19. International Agency for Research on Cancer, Lyon, France.
- Johnstone, R. A. W., P. M. Quan, and W. Carruthers. 1962. Composition of cigarette smoke: Some low-boiling components. Nature 195:1267-1269.
- Kinlin, T. E., R. Muralidhara, A. O. Pittet, A. Sanderson, and J. P. Walratt. 1972. Volatile components of roasted filberts. J. Agric. Food Chem. 20:1021-1028.
- Lapkin, M. 1965. Epoxides. Pp. 263-293 in H. F. Mark, J. J. McKetta, Jr., and D. F. Othmer, eds. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd edition, Volume 8. Interscience, New York.
- Lee, B. B., G. E. Wilkins, and E. M. Nichols. 1979. Organic Solvent Use Study. Report No. EPA-560/12-79-002. (Available from National Technical Information Service, Springfield, Va., as PB-301 342.) Radian Corporation, Austin, Tex. 245 pp.
- Lee, H., and K. Neville. 1967. Handbook of Epoxy Resins. McGraw-Hill, New York. [899] pp.
- Levy, A., S. E. Miller, and F. Scofield. 1971. The photochemical smog reactivity of solvents. Pp. 305-316 in H. Englund and W. T. Berry, eds. Proceedings of the Second International Clean Air Congress, New York.
- Mackay, D., and P. J. Leinonen. 1975. Rate of evaporation of low-solubility contaminants from water bodies to atmosphere. Environ. Sci. Technol. 9:1178-1180.

- Mäler, K. G. 1977. A note on the use of property values in estimating marginal willingness to pay for environmental quality. *J. Environ. Econ. Manage.* 4:355-369.
- Mara, S. J., E. C. So, and B. E. Suta. 1979. Uses, Sources and Atmospheric Emissions of Alkylbenzene Derivatives. Final report. Prepared for the U.S. Environmental Protection Agency, Contract No. 68-02-2835, by SRI International. SRI Project CRU-6780-NS. Standard Research Institute International, Menlo Park, Calif. 64 pp.
- Maynard, J. B., and W. N. Sanders. 1969. Determination of the detailed hydrocarbon composition and potential atmospheric reactivity of full-range gasolines. *J. Air Pollut. Control Assoc.* 19:505-510.
- Mayrsohn, H., and F. Bonamassa. 1971. The hydrocarbon composition of Los Angeles gasolines, 1970. *Am. Chem. Soc., Div. Pet. Chem., Prepr.* 16(4):D73-D76.
- Mayrsohn, H., J. H. Crabtree, M. Kuramoto, R. D. Sothern, and S. H. Mano. 1977. Source reconciliation of atmospheric hydrocarbons 1974. *Atmos. Environ.* 11:189-192.
- Mayrsohn, H., M. Kuramoto, J. H. Crabtree, and R. D. Sothern. 1978. Hydrocarbon Composition of Los Angeles Gasolines. California State Air Resources Board, El Monte, Calif.
- McAllister, S. H. 1955. Industrial applications of aromatic alkylation. P. 589 in B. T. Brooks, C. E. Boord, S. S. Kurtz, Jr., and L. Schmerling, eds. *The Chemistry of Petroleum Hydrocarbons*, Volume 3. Reinhold, New York.
- McAuliffe, D. 1977. Evaporation and solution of C_2 to C_{10} hydrocarbons from crude oils in the sea surface. Pp. 363-372 in D. A. Wolfe, ed. *Fate and Effects of Petroleum Hydrocarbons in Marine Organisms and Ecosystems*. Pergamon Press, New York.
- Miale, J. N., and P. B. Weisz. 1971. Hydrocarbon conversion over crystalline aluminosilicates containing S, Se, and Te. *J. Catalysis* 20:288-292.
- Moacanin, J., G. Holden, and N. W. Tschoegl, eds. 1969. *Block Copolymers*. Wiley Interscience, New York. 209 pp.
- Molau, G. E. 1965. Heterogeneous polymer systems. I. Polymeric oil-in-oil emulsions. *J. Polymer Sci., Part A*, 3:1267-1278.

- Morris, W. E., and K. T. Dishart. 1971. Influence of vehicle emission control systems on the relationship between gasoline and vehicle exhaust hydrocarbon composition. Pp. 63-93, and discussion, pp. 94-101 in Effect of Automotive Emission Requirements on Gasoline Characteristics. ASTM Special Publication 487. American Society for Testing and Materials, Philadelphia, Penna.
- MSA Research Corporation. 1972. Hydrocarbon Pollutant Systems Study. Volume I. Stationary Sources, Effects and Control. Final report. Report No. APTD-1499. (Available from National Technical Information Service, Springfield, Va., as PB-219 073.) MSA Research Corporation, Evans City, Penna. 377 pp.
- Myers, M. E., Jr., J. Stollsteimer, and A. M. Wims. 1975. Determination of hydrocarbon-type distribution and hydrogen/carbon ratio of gasolines by nuclear resonance spectrometry. Anal. Chem. 47:2010-2015.
- National Academy of Sciences. 1973. Report by the Committee on Motor Vehicle Emissions. In accordance with Section 202(c) of the Clean Air Amendment of 1970 and in partial fulfillment of Contract No. 68-01-0402 between the U.S. Environmental Protection Agency and the National Academy of Sciences. Division of Engineering, National Academy of Sciences, Washington, D.C. 140 pp.
- National Academy of Sciences. 1974. An Evaluation of Catalytic Converters for Control of Automobile Exhaust Pollutants. Consultant report to the Committee on Motor Vehicle Emissions, National Research Council, National Academy of Sciences, Washington, D.C. 116 pp.
- National Academy of Sciences. 1975. Petroleum in the Marine Environment. Workshop on Inputs, Fates, and the Effects of Petroleum in the Marine Environment, May 21-25, 1973, Airlie, Va. National Academy of Sciences, Washington, D.C. 107 pp.
- National Academy of Sciences. 1976. Vapor-Phase Organic Pollutants. Report by the Committee on Medical and Biologic Effects of Environmental Pollutants, National Research Council, National Academy of Sciences, Washington, D.C. xiii + 411 pp.
- National Petroleum Council. 1971. Environmental Conservation: The Oil and Gas Industries. A Summary. Volume 1. National Petroleum Council, Washington, D.C. 106 pp.
- Nursten, H. E., and M. R. Sheen. 1974. Volatile flavour components of cooked potato. J. Sci. Food Agric. 25:643-663.
- Paul, S. K., and S. L. Soder. 1979. Ethylbenzene-salient statistics. Pp. 645.3000 H-J [loose-leaf] in Chemical Economics Handbook.

- Price, G. L., Z. R. Ismagilov, and J. W. Hightower. 1980. Dehydrocyclization of n-Paraffins over Te-NaX Zeolite Catalysts. Paper presented at the 7th International Congress on Catalysis, Tokyo, Japan, June 30-July 4, 1980. [10] pp.
- Rasmussen, R. A., and F. W. Went. 1965. Volatile organic material of plant origin in the atmosphere. *Proc. Nat. Acad. Sci. U.S.A.* 53:215-220.
- Rosen, S. 1974. Hedonic prices and implicit markets: Product differentiation in pure competition. *J. Pol. Econ.* 82:34-55.
- Sexton, K., and H. Westberg. 1980. Ambient hydrocarbon and ozone measurements downwind of a large automotive painting plant. *Environ. Sci. Technol.* 14:329-332.
- Shackelford, W. M., and L. H. Keith. 1976. Pp. 213-214 in *Frequency of Organic Compounds Identified in Water*. [Report] EPA-600/4-76-062. U.S. Environmental Protection Agency, Office of Research and Development, Environmental Research Laboratory, Athens, Ga.
- Sherwin, M. B. 1979. Development in aromatics derivatives technology. *Chem. Eng. Progress* 75:26.
- Simpson, D. W. 1966. Extrusion of foamed plastic sheet material. Belgian Patent 671,085. Dow Chemical Co. [Chem. Abs. 66:66276p, 1967].
- Smith, C. L., and W. G. MacIntyre. 1971. Initial aging of fuel oil films on seawater. Pp. 457-461 in *Proceedings of a Joint Conference on Prevention and Control of Oil Spills*, June 15-17, 1971, Sheraton Park Hotel, Washington, D.C. Sponsored by the American Petroleum Institute, the Environmental Protection Agency, and the U.S. Coast Guard, Washington, D.C.
- Southern California Association of Governments and South Coast Air Quality Management District, Los Angeles. 1979. *Air Quality Management Plan*. 773 pp.
- Stanford Research Institute. 1977. *Chemical Origins and Markets*. 5th Edition. Chemical Information Services, Stanford Research Institute International, Menlo Park, Calif. 118 pp.
- Stevens, K. L., J. L. Bomben, and W. H. McFadden. 1967. Volatiles from grapes. *Vitis vinifera* (Linn.) cultivar Grenache. *J. Agric. Food Chem.* 15:378-380.

- Suta, B. E. 1979. Nonoccupational Exposures to Alkylbenzenes from Their Use as Solvents [SRI draft report to the U.S. Environmental Protection Agency, December 1979]. Stanford Research Institute International, Menlo Park, Calif. [57] pp.
- Sutton, C., and J. A. Calder. 1975. Solubility of alkylbenzenes in distilled water and seawater at 25.0°C. J. Chem. Eng. Data 20: 320-322.
- Thayer, M., and W. D. Schulze. 1980. An Examination of Benefits and Costs of Achieving Ambient Standards in the South Coast Air Basin. U.S. Environmental Protection Agency, Washington, D.C.
- Tossavainen, A. 1978. Styrene use and occupational exposure in the plastics industry. Scand. J. Work Environ. Health 4(Suppl. 2): 7-13.
- U.S. Bureau of the Census. 1977. U.S. Exports, Schedule B Commodity Groupings, Schedule B Commodity by Country. [Report]FT 410/December 1977. Issued March 1978. U.S. Government Printing Office, Washington, D.C. [636] pp.
- U.S. Bureau of the Census. 1979. U.S. Exports, Schedule E. Commodity by Country. [Report]FT410/December 1978. Issued February 1979. U.S. Government Printing Office, Washington, D.C. [650] pp.
- U.S. Department of Health, Education, and Welfare. 1979. Smoking and Health. A Report of the Surgeon General. PHS 79-50066. Public Health Office of the Assistant Secretary for Health, Office on Smoking and Health, U.S. Department of Health, Education, and Welfare, Washington, D.C. 1219 pp.
- U.S. Environmental Protection Agency. 1977a. Atmospheric Benzene Emissions. Report No. EPA-450/3-77-029. Prepared by PEDCO Environmental, Inc., Cincinnati, Ohio for the U.S. Environmental Protection Agency, Research Triangle Park, N.C.
- U.S. Environmental Protection Agency, 1977b. Compilation of Air Pollutant Emission Factors. 3rd Edition. U.S. Environmental Protection Agency, Research Triangle Park, N.C.
- U.S. Environmental Protection Agency. 1978a. Air Quality Criteria for Ozone and Other Photochemical Oxidants. EPA-600/8-78-004. U.S. Environmental Protection Agency, Office of Research and Development, Washington, D.C. 341 pp.

- U.S. Environmental Protection Agency. 1978b. First Annual Report--1977. Administration of the Toxic Substances Control Act. U.S. Environmental Protection Agency, Washington, D.C. i + 17 pp.
- U.S. Food and Drug Administration. 1977. Food and drugs. U.S. Code Fed. Regul., Title 21, pp. 376-608.
- U.S. International Trade Commission. 1976. Synthetic Organic Chemicals, United States Production and Sales, 1974. USITC Publication 776. U.S. Government Printing Office, Washington, D.C. 256 pp.
- U.S. International Trade Commission. 1977. Synthetic Organic Chemicals, United States Production and Sales, 1976. USITC Publication 833. U.S. Government Printing Office, Washington, D.C. 357 pp.
- U.S. International Trade Commission. 1979. Synthetic Organic Chemicals, United States Production and Sales, 1978. USITC Publication 1001. U.S. Government Printing Office, Washington, D.C.
- U.S. International Trade Commission. 1980. Preliminary Report on U.S. Production of Selected Synthetic Organic Chemicals (Including Synthetic Plastics and Resin Materials) Preliminary Totals, 1979. U.S. International Trade Commission, Washington, D.C. 9 pp.
- Vanzo, E. 1966. Ordered structures of styrene-butadiene block copolymers. J. Polymer Sci., Part A-1, 4:1727-1730.
- Walter, P. 1976. Air Pollution Assessment of Toluene. Report No. MTR-7215. (Available from National Technical Information Service, Springfield, Va., as PB-256 735.) Mitre Corporation, McLean, Va. 92 p.
- Walradt, J. P., A. O. Pittet, T. E. Kinlin, R. Muralidhara, and A. Sanderson. 1971. Volatile components of roasted peanuts. J. Agric. Food Chem. 19:972-979.
- Ward, D. J. 1965. Cumene. Pp. 543-546 in H. F. Mark, J. J. McKetta, Jr., and D. F. Othmer, eds. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd edition, Volume 6. Interscience, New York.
- Wigg, E. E., R. J. Campion, and W. L. Peterson. 1972. The effect of fuel hydrocarbon composition on exhaust hydrocarbon and oxygenate emissions. Technical Paper 72051. Society of Automotive Engineers, Warrendale, Penna. 13 pp.
- Ziemba, G. P. 1964. Acrylonitrile-styrene copolymers. Pp. 425-435 in H. F. Mark, N. G. Gaylord, and N. M. Bikales, eds. Encyclopedia of Polymer Science and Technology: Plastics, Resins, Rubbers, Fibers, Volume 1. Interscience, New York.
- Zimmerman, R. L., and W. E. O'Connor. 1967. A continuous preparation of thermal plastic copolymers and terpolymers of unsaturated cyclic

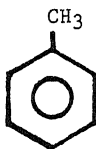
CHAPTER 2

PHYSICAL AND CHEMICAL PROPERTIES

The aromatic hydrocarbons are classified into three principal groups according to the number of benzene rings and the type of linkage between the rings in the molecule. These groups are: benzene and its aliphatic and alicyclic derivatives; polyphenyls, which have two or more uncondensed rings; and polynuclear compounds, i.e., those with two or more condensed rings.

Benzene and its alkyl derivatives fall into the first group. These pungent liquids are volatile and exert high vapor pressure at room temperature. The properties of individual compounds within this group are described in the following pages.

TOLUENE



Chemical Abstracts No. 108-88-3
(Chemical Abstracts Service, 1977)

Toluene is the second member of the homologous aromatic series of compounds. It is a colorless liquid and has a distinctive aromatic odor that is similar to but milder than that of benzene. Some synonyms for this compound are toluol, methylbenzene, and phenylmethane.

Physical Properties

Some important physical and thermodynamic properties of toluene are presented in Table 2-1.

Chemical Properties

Most of the reactions of toluene are similar to those of benzene. As shown in Table 2-2, its substitution reactions are the exception. They occur faster with toluene than with benzene (Nelson, 1955).

TABLE 2-1. Physical and Thermodynamic Properties of Toluene

Property	Value	Property	Value
Molecular weight ^a	92.13	Critical properties: ^b	
Boiling point, 760 mm Hg, °C ^b	110.6	Temperature, °C	320.
Freezing point, °C ^b	-94.991	Pressure, atm	40.
Density at 25°C, g/ml ^a	0.8623	Density, g/ml	0.
Refractive index at 25°C ^a	1.4941	$\frac{PV}{RT}$	0.
Vapor density (air = 1) ^a	3.20	Heat of vaporization at 25°C, kcal/mol ^b	9.
Percent in saturated air (at 760 mm Hg and 26°C) ^c	3.94	Heat of fusion, kcal/mol ^b	1.
Specific dispersion ^c		Heat of formation, kcal/mol: ^b	
Solubility:		Liquid	2.8
In distilled water at 25°C, mg/l ^d	534.8 ± 4.9	Gas	11.9
In seawater at 25°C, mg/l ^d	379.3 ± 2.8	Entropy at 25°C, cal/(mol)(°C):	
In ethyl alcohol ^a	Miscible	Liquid ^f	52.4
In ethyl ether ^a	Miscible	Gas ^b	76.4
Flammable limits (% by volume in air) ^c	1.17 - 7.10	Free energy of formation, kcal/mol: ^b	
Flash point (closed cup) ^c			

y	Value
---	-------

on coefficient (K_p)^g in
r and water at 20.06°C)^h

5.14

on coefficient (K_D)ⁱ in
nol and water^j

512 ± 22

reshold, ppm^k

2.14

ion factors (in air at 25°C)

1 ppm = 3.77 mg/m³
1 mg/m³ = 0.265 ppm

of spectral properties:

aviolet^l

ared^m

ear magnetic resonance^{n,o}

l

, 1978

r and Scott, 1943

ni et al., 1953

n and Calder, 1975

essibility factor

y, 1929

^gK_p = Concentration in water
Concentration in vapor

^hHanson and Ismail, 1975

ⁱK_D = Concentration in octanol
Concentration in water

^jHansch and Leo, 1979

^kSax and Sax, 1974

^lGrasselli and Ritchey, 1975a

^mPouchert, 1975

ⁿBhacca et al., 1962

^oPouchert and Campbell, 1974

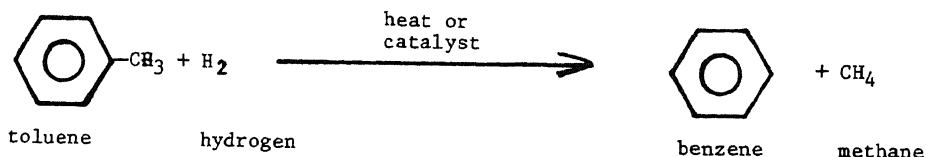
TABLE 2-2. Relative Rates of Substitution in Benzene and Toluene^a

Reaction	Conditions	Ratio of Reactivity of k_{toluene} to k_{benzene}
Bromination	Bromine (Br_2) in acetic acid (HOAc) ^b with iodine (I_2): At 25°C At 45°C	467 272
Chlorination	Chlorine (Cl_2) in acetic acid at 24°C	353
Chloromethylation	Formaldehyde (CH_2O) in acetic acid at 60°C with zinc chloride (ZnCl_2) and hydrochloric acid (HCl)	112
Nitration	Acetyl nitrate (AcONO_2) in acetic anhydride (Ac_2O) at 0°C Acetyl nitrate in acetic anhydride at 30°C Nitric acid (HNO_3) in nitromethane (CH_3NO_2) at 30°C	27 23 21
Acetylation	Acetyl chloride (AcCl) with aluminum chloride (AlCl_3) at 0°C Acetyl chloride with aluminum chloride at 50°C	13.3 8.4
Benzoylation	Benzoyl chloride with ($\text{C}_6\text{H}_5\text{COCl}$) aluminum chloride at 25°C	120-200
Mercuration	Mercuric acetate $\text{Hg}(\text{OAc})_2$ in acetic acid with perchloric acid (HClO_4): At 25°C At 50°C At 75°C	7.9 7.0 5.9
Sulfonation	Sulfuric acid (H_2SO_4) in picolinic acid ($\text{C}_6\text{H}_5\text{NO}_2$) at 40°C	5.1
Brosylation	p-Bromobenzenesulfonyl chloride ($\text{p-BrC}_6\text{H}_4\text{SO}_2\text{Cl}$) with aluminum chloride at 25°C	3.7
Methylation	Methyl bromide (CH_3Br) with aluminum bromide (AlBr_3) at 0°C	3.5
Isopropylation	Propylene ($\text{CH}_3\text{CH}=\text{CH}_2$) with aluminum chloride in nitromethane at 40°C	2.1

^aData from Nelson, 1955.

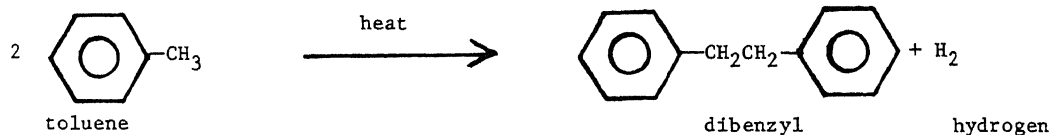
^b $\text{Ac} = \text{CH}_3-\text{C}-$, acetyl group.
 $\begin{array}{c} || \\ \text{O} \end{array}$

The presence of a methyl group ($-\text{CH}_3$) offers additional possibilities for reaction. The most important is dealkylation to produce benzene (Bradsher, 1977):

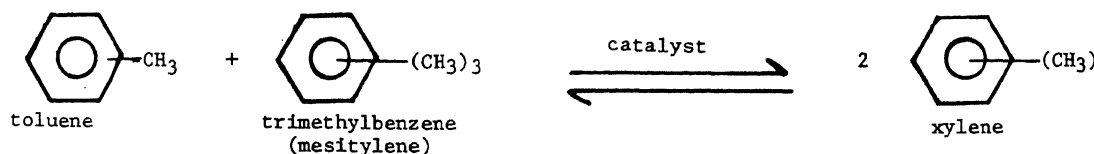
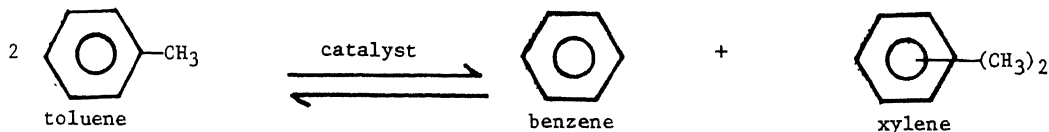


A number of catalytic and thermal commercial processes are used to produce toluene. All of them are implemented in the vapor phase at high temperatures under pressures greater than 20 atm.

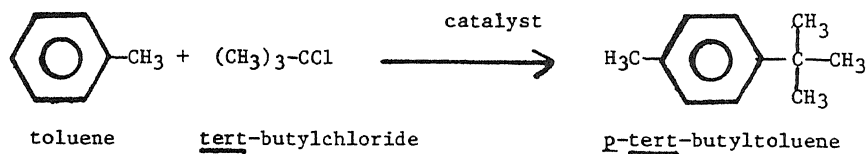
Under certain thermal conditions, toluene forms dibenzyl (Cier, 1969):



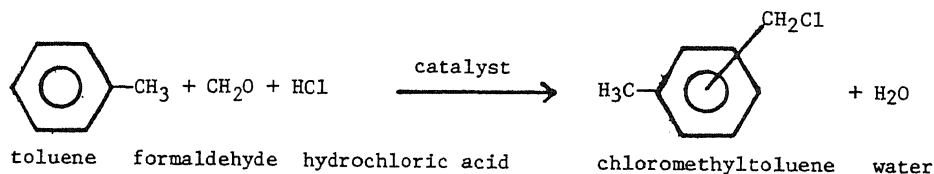
In the absence of a catalyst, toluene also undergoes disproportionation and transalkylation. These reactions are reversible and can be carried out in either the liquid or the vapor phase.



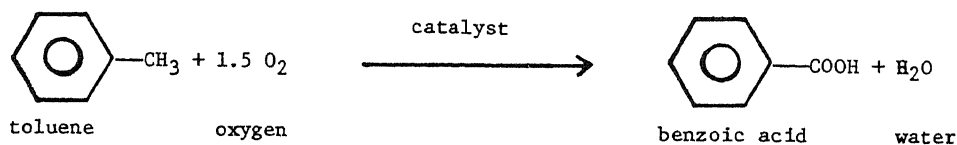
Toluene can be alkylated readily in the presence of certain
dic catalysts:



undergo chloromethylation with formaldehyde (Cier, 1969):

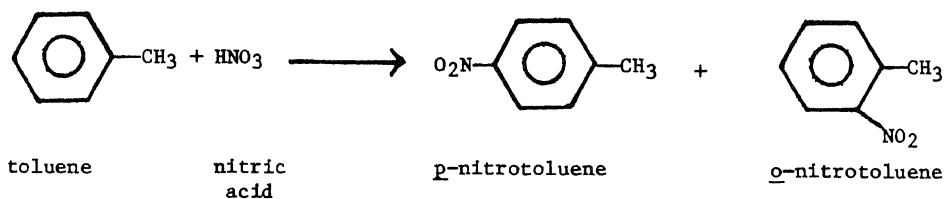


In the liquid phase, toluene is oxidized with air, yielding
zoic acid as the principal product. Catalysts are generally used
this reaction (Cier, 1969):



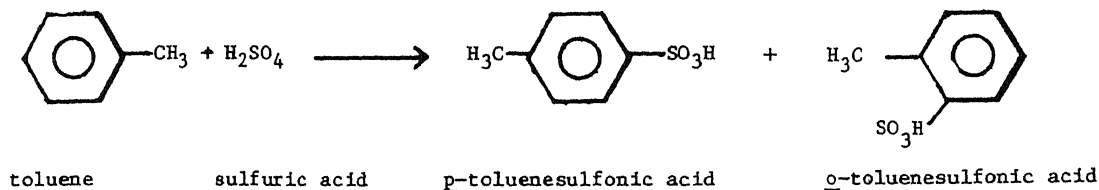
The methyl group can also be oxidized with various oxidizing
nts, but these reactions are not used commercially.

Nitration is effected much more easily with toluene than with
zene. The principal product from mononitration is a mixture of
and p-nitrotoluenes. Very little of the meta compound is formed
er, 1969):

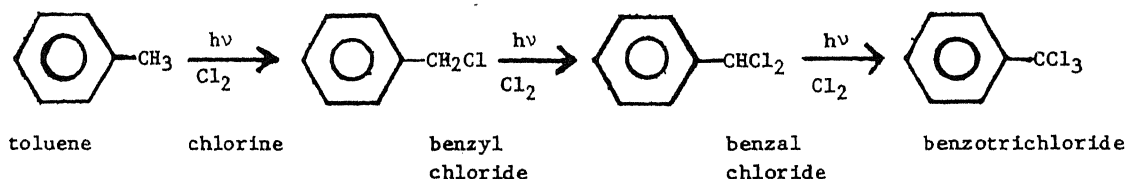


Nitration is generally conducted with a mixture of concentrated nitric and sulfuric acids. The dinitration of toluene leads to the formation of 2,4- and 2,6-dinitrotoluenes, which are intermediates in the manufacture of toluene diisocyanate (TDI). At high temperatures, when a large quantity of nitric acid is used, 2,4,6-trinitrotoluene (TNT) is formed as the major product (Chadwick and Hardy, 1967).

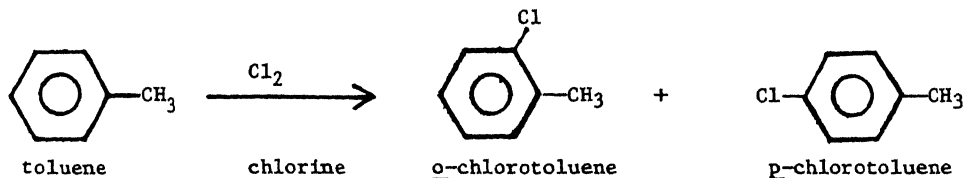
Sulfonation of toluene also produces a mixture of the o- and p-toluenesulfonic acids (Cier, 1969):



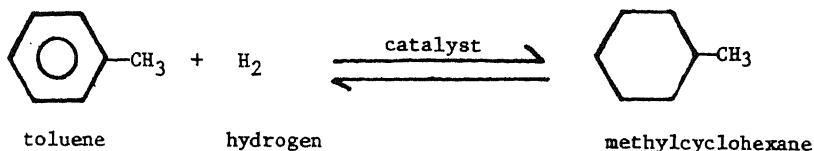
When exposed to actinic light, halogens react with toluene to yield methyl substitution products (Gait, 1967):



However, in the absence of light, halogenation catalysts react with toluene to produce a mixture of o- and p-chlorotoluenes. The nuclear halogens do not react readily with chlorine:



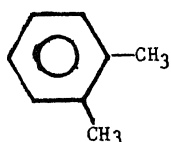
Toluene can be readily hydrogenated to form methylcyclohexane:



Badger and Spotswood (1960) passed toluene vapor with nitrogen through a silica tube filled with porcelain chips at 700°C. They reported that the pyrolysis products included some known and suspected carcinogenic aromatic hydrocarbons (Table 2-3) (Christensen et al., 1976).

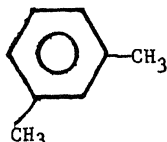
XYLENES AND ETHYLBENZENE

The xylenes and ethylbenzene each contain eight carbon atoms:



o-xylene

Chemical Abstracts
No. 95-47-6
(Chemical Abstracts
Service, 1977)



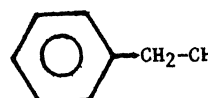
m-xylene

Chemical Abstracts
No. 108-38-3
(Chemical Abstracts
Service, 1977)



p-xylene

Chemical Abstracts
No. 106-42-3
(Chemical Abstracts
Service, 1977)



ethylbenzene

Chemical Abstracts
No. 100-41-4
(Chemical Abstracts
Service, 1977)

The term "xylenes" generally applies to a mixture of any two or three of the dimethylbenzene isomers: o-, p-, and m-xylenes. "Mixed xylenes" can refer to the same mixtures but is often used when ethylbenzene is also present.

The relative proportions of the o, m, and p isomers in such mixtures, which are the most common commercial products, vary with the production source. They are found in the following ranges: o-xylene, ~10% to 25%; m-xylene, ~45% to 70%; and p-xylene, ~6% to 15%. The mixtures can contain such impurities as toluene, trimethylbenzene, phenol, thiophene, pyridine, and nonaromatic hydrocarbons (U.S. Department of Health, Education, and Welfare, 1975). Separation can be achieved by fractional crystallization of p-xylene at -3.9°C and fractional distillation of m-xylene, leaving o-xylene in the still (Cier, 1970).

TABLE 2-3. Compounds Identified in Tars Produced by the Pyrolysis of Toluene

<u>Compound</u>	<u>Weight, % of tar formed</u>	<u>Compound</u>	<u>Weight, tar for</u>
Anthracene	0.009	4,4'-Dimethylbiphenyl	0.99
1,2-Benzanthracene ^b	0.014	Biphenyl	0.27
Benzene ^b	2.54	Fluoranthene	Trace
3,4-Benzofluoranthene ^b	0.002	Fluorene	0.085
10,11-Benzofluoranthene ^b	Trace	Naphthalene	0.042
11,12-Benzofluoranthene ^b	Trace	Phenanthrene	0.12
1,2-Benzofluorene	0.007	Pyrene	Trace
2,3-Benzofluorene	0.017	Stilbene	0.44
1,2-Benzopyrene ^b	0.002	Styrene	0.11 ^c
3,4-Benzopyrene ^b	0.002	Toluene	93.5
Chrysene ^b	0.03	<u>p</u> -Xylene	0.05
Alkylchrysene	Trace	Resins and losses	0.7
Bibenzyl	1.00		

^aData from Badger and Spotswood, 1960.^bSuspected carcinogen (Christensen et al., 1976).^cMixture of o-xylene and styrene.

Physical Properties

Many properties of the individual isomers of xylene are very similar (Table 2-4). Consequently, it is difficult to produce individual components with very high purity. Since there is a great demand for pure xylenes, especially p-xylene, much effort has been directed toward accomplishing these separations. As a result, the physical and chemical processes of the xylenes have been studied and evaluated in greater depth than they have for many organic compounds.

Of great practical importance, of course, are the distillation characteristics of these isomers. Whereas o-xylene can be separated readily from m-xylene by distillation, it is only with difficulty that ethylbenzene can be distilled from p-xylene in pure form. It is also difficult to separate p-xylene from m-xylene by distillation (Cier, 1970).

Solubility data for water in these aromatic compounds and for these compounds in water are given in Table 2-5 (American Petroleum Institute, 1966).

Chemical Properties

Chemical reactions of these aromatic compounds can be divided into three classes: Class 1 reactions involve the number and position of the alkyl groups; Class 2 includes chemical reactions of the alkyl groups; and Class 3 reactions involve the aromatic ring. Class 1 is of primary interest in the production of pure individual isomers. The second class dominates the transformation of the pure isomers into products of commercial interest. The third group of reactions also produces new products from the parent isomer, but they are not of major commercial interest.

Class 1 Reactions: McCaulay and Lien (1952), Norris and Vaala (1939), and Pitzer and Scott (1943) studied the isomerization of xylenes in the liquid phase. Using various halide catalysts at temperatures between 50°C and 120°C, they found no ethylbenzene in the products of these reactions.

In the presence of large amounts of boron trifluoride, the xylenes form a complex and remain in the acid phase. In the protonated form, the xylenes isomerize almost exclusively to form the meta isomer. The amount of uncomplexed xylenes in the hydrocarbon phase is governed by the thermodynamic equilibrium (Cier, 1970).

At temperatures between 0°C and 30°C, kinetic studies of the isomerization of o- and p-xylene in an excess of boron trifluoride showed no disproportionation (McCaulay and Lien, 1952). The primary product in each case was m-xylene.

Property	o-Xylene	m-Xylene	p-Xylene	Ethylbenzene
Molecular weight ^a	106.16	106.16	106.16	106.16
Boiling point, 760 mm, °C ^b	144.411	139.103	138.351	136.186
Freezing point, °C ^b	-25.182	-47.872	13.263	-94.975
Density at 25°C, g/ml ^a	0.87596	0.85990	0.85669	0.86264
Refractive index at 25°C ^a	1.50295	1.49464	1.49325	1.49320
Vapor density (air = 1) ^a	3.7	3.66	3.7	3.66
Percent in saturated air (at 760 mm Hg) ^c	1.32 (32°C)	1.32 (28.3°C)	1.32 (27.3°C)	1.32 (26°C)
Specific dispersion ^c	180.3	181.1	181.8	174.6
Solubility:				
In distilled water at 25°C, mg/l ^d	170.5 ± 2.5	146.0 ± 1.6	156.0 ± 1.6	161.2 ± 0.9
In seawater				
at 25°C, mg/l ^c	129.6 ± 1.8	106.0 ± 0.6	110.9 ± 0.9	111.0 ± 1.3
In ethyl alcohol ^a	Very soluble	Very soluble	Very soluble	Miscible
In ethyl ether ^a	Very soluble	Very soluble	Very soluble	Miscible
Flammable limits, % by volume in air ^c	1.09-6.40	1.09-6.40	1.08-6.60	0.99-6.70

Property	o-Xylene	m-Xylene	p-Xylene	Ethylbenzene
Flash point (closed cup) ^c	17.2°C	25°C	25°C	17.2°C
Vapor pressure at 25°C, mm Hg ^b	6.6	8.39	8.87	9.57
Critical properties: ^b				
Temperature, °C	359.0	346.0	345.0	346.4
Pressure, atm	36	35	34	37
Density, g/ml	0.28	0.27	0.29	0.29
PV/R ^e	0.26	0.27	0.25	0.26
Heat of vaporization at 25°C, kcal/mol ^b	10.470	10.160	10.110	10.097
Heat of fusion, kcal/mol ^b	3.250 + 0.010	2.784 + 0.015	4.090 + 0.020	2.190
Heat of combustion at 25°C, kcal/mol ^b	1,088.16	1,087.92	1,088.16	1,091.03
Heat of formation at 25°C, liquid, kcal/mol ^b	-5.841	-6.075	-5.838	-2.977
Entropy at 25°C, cal/deg/mol:				
Liquid ^f	58.80	60.42	59.20	60.66
Gas ^b	84.50 + 0.3	85.55 + 0.4	84.27 + 0.3	85.65 + 0
Free energy of formation, liquid, kcal/mol ^b	26.370	25.730	26.310	28.614

TABLE 2-4. Physical and Thermodynamic Properties of Xylene and Ethylbenzene (cont'd)

Property	<u>o-Xylene</u>	<u>m-Xylene</u>	<u>p-Xylene</u>	<u>Ethylbenzene</u>
Partition coefficient (K_D) ^g in octanol and water ^h	589	1,585	1,413	1,413
Conversion factors for the three isomeric xylenes and ethylbenzene, in air at 25°C	1 ppm = 4.34/m ³ ; 1 mg/m ³ = 0.230 ppm			
Sources of spectral properties:				
Ultraviolet ⁱ				
Infrared ^j				
Nuclear magnetic resonance ^{k,l}				
Mass ^h				
^a Weast, 1978	^f Kelley, 1929	ⁱ Grasselli and Ritchey, 1975a		
^b Pitzer and Scott, 1943	^g K_D = <u>Concentration in octanol</u>	^j Pouchert, 1975		
^c Rossini <u>et al.</u> , 1953	<u>Concentration in water</u>	^k Bhacca <u>et al.</u> , 1962		
^d Sutton and Calder, 1975	^h Leo <u>et al.</u> , 1971	^l Pouchert and Campbell, 1974		
^e Compressibility factor				

TABLE 2-5. Solubility Data for Water and the Xylenes and Ethylbenzene,
Mol Fraction^a

<u>Temperature,</u> <u>°C</u>	<u>Water in</u> <u>Xylenes</u>	<u>Water in</u> <u>Ethylbenzene</u>	<u>Xylenes in</u> <u>Water</u>	<u>Ethylbenzene</u> <u>in Water</u>
10	0.0017	NR ^b	0.000034	0.000036
26.67	0.0031	0.0026	0.000033	0.000035
37.78	NA	0.0038	0.000035	0.000037
65.56	NA	0.0080	0.000052	0.000058

^aData from the American Petroleum Institute, 1966.

^bNot reported.

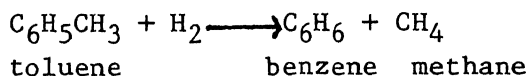
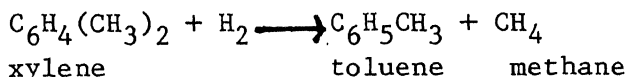
Pitts et al. (1955) studied vapor-phase isomerization of xylene with different catalysts at temperatures higher than 380°C. Using platinum on a silica-alumina catalyst at 13 atm, an equilibrium mixture of xylene was produced from m-xylene. The investigators found no ethylbenzene. A silica-alumina catalyst at low pressures (between 0.1 and 1.0 atm) resulted in the conversion of small amounts of m-xylene to ethylbenzene (Boedeker and Erner, 1954). Using tungsten-molybdena on a silica-alumina catalyst at high pressures (10 atm), Becker et al. (1966) observed that the presence of ethylbenzene inversely affected the extent of xylene isomerization.

Ethylbenzene does not readily isomerize to xylene. The negative temperature coefficient shown by ethylbenzene suggests that an intermediate whose concentration is inversely proportional to temperature is involved in this overall reaction. A likely compound would be a hydrogenated aromatic (McCaulay and Lien, 1952).

Using a silica-alumina cracking catalyst at 515°C and a mixture of xylenes and ethylbenzene at 90 mm Hg, Boedeker and Erner (1954) observed isomerization, but very little disproportionation. At 760 mm Hg, there was considerable disproportionation. Hoff (1958) and McCaulay et al. (1957) studied disproportionation of ethylbenzene and m-xylene with a hydrogen fluoride-boron trifluoride catalyst. In these reactions, disproportionation is a function of the boron trifluoride concentration up to an equimolar ratio of the boron trifluoride to the aromatic. The migration of ethyl groups is much faster than that of the methyl groups (Lien and McCaulay, 1953; McCaulay and Lien, 1957). In the presence of a large quantity of hydrogen fluoride-boron trifluoride catalyst, almost complete disproportionation of ethylbenzene occurs at 0°C. At 66°C, m-xylene is unreactive, but at higher temperatures it disproportionates.

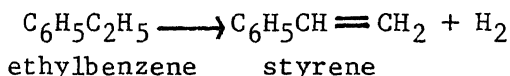
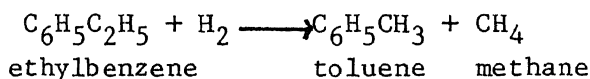
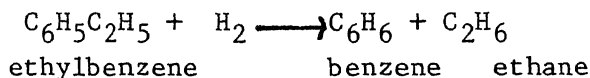
Under certain conditions, ethylbenzene will preferentially dealkylate xylenes without disproportionation of the xylenes. However, there is some disproportionation of the ethylbenzene. The rate at which ethylbenzene disappears by its interaction with xylene is greatest with the ortho derivative and least with p-xylene.

Silsby and Sawyer (1956) have studied dealkylation of xylenes in the presence of hydrogen. They concluded that the reaction is principally thermal, that pressure has little effect on the degree of conversion, and that the reaction products are consistent with the idea of two consecutive reactions:



Tsuchiya et al. (1959, 1960) conducted extensive studies of the alkylolation rates of the individual isomers of xylene at temperatures between 590°C and 680°C at 10 to 40 atm. A 3:11 molar ratio of hydrogen hydrocarbon was used at contact times of 10 to 60 seconds. The alkylolation rates of the xylene isomers followed 1.5 order kinetics.

The dealkylation of ethylbenzene under similar conditions is much more complex. At least three reactions are encountered (Cier, 1970):



The production of styrene has been observed only at pressures less than 20 atm (Cier, 1970). Because the reaction is complex, kinetic analysis is difficult. The rate at which ethylbenzene is dealkylated under these conditions appears to be slightly greater than it is for xylenes.

Dealkylation of highly aromatic extracts from a kerosene fraction results in a number of different aromatic products (Bethea et al., 1963). Operating conditions can be adjusted to maximize the production of benzene, toluene, xylenes, or ethylbenzene. There is a large degradation of the aromatic extracts that are fed in such operations since only 50% to 65% is recovered as liquid product.

Class 2 Reactions. From an industrial viewpoint, the most important reactions of the xylenes or ethylbenzene are those involving the oxidation of the methyl groups and the dehydrogenation of the methyl group.

Ethylbenzene is catalytically dehydrogenated to yield styrene and hydrogen. Thermodynamically, high temperatures and low pressures favor the dehydrogenation. With certain catalysts, the available hydrogen and carbon dioxide are converted via the water-gas shift reaction to carbon monoxide and water. The removal of hydrogen by a secondary reaction causes a substantial increase in the conversion of ethylbenzene to styrene (Olson, 1968).

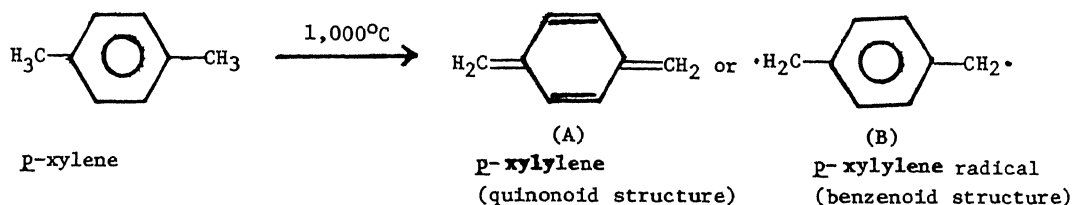
Ethylbenzene can also be oxidatively dehydrogenated to produce styrene. Oxygen, halogens (especially iodine), and sulfur dioxide have been used in this reaction as hydrogen acceptors (Adams, 1967; Cier, 1970). Apparently, conversion and selectivity vary quite widely with the nature of the oxidizing agent and the reaction conditions.

A second approach to the oxidation of ethylbenzene involves the production of hydroperoxide (Cier, 1970). This is accomplished by blowing air at pressures less than 50 psig at approximately 149°C. When there is a >80% selectivity for the hydroperoxide, less than 10% of ethylbenzene is converted. The hydroperoxide is then reacted with propylene to give propylene oxide and 1-phenylethyl alcohol, which is dehydrated to produce styrene.

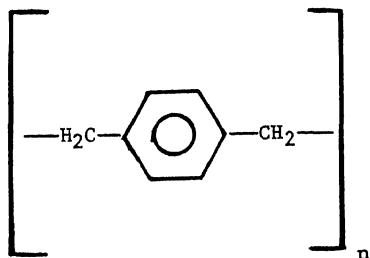
The pure isomers of the xylenes are oxidized much more frequently than mixtures of the xylenes. All isomers have been oxidized in the liquid phase. These oxidations are usually conducted with air between 100°C and 300°C. Pressures may vary up to 40 atm and reaction times up to 3 hr. The reaction is highly exothermic, e.g., the heat of reaction for p-xylene is 326 kcal/mol (Cier, 1970). The desired product in each case is the dicarboxylic acid. When p-xylene is used, the dimethyl ester form of the acid is sometimes produced.

Combustion experiments show that o-xylene is oxidized much faster than the meta or para isomers. This difference is related to the reactivities of the different radicals involved in the chain-branching phenomenon (Barnard and Sankey, 1968).

Pyrolysis of xylenes may lead to interesting products. When subjected to temperatures higher than 1,000°C, p-xylene forms p-xylylene which is a prototype of a class of hydrocarbons known as Chichibabin hydrocarbons. These compounds may be represented either by a quinonoid structure (A) or by a benzenoid biradical structure (B):



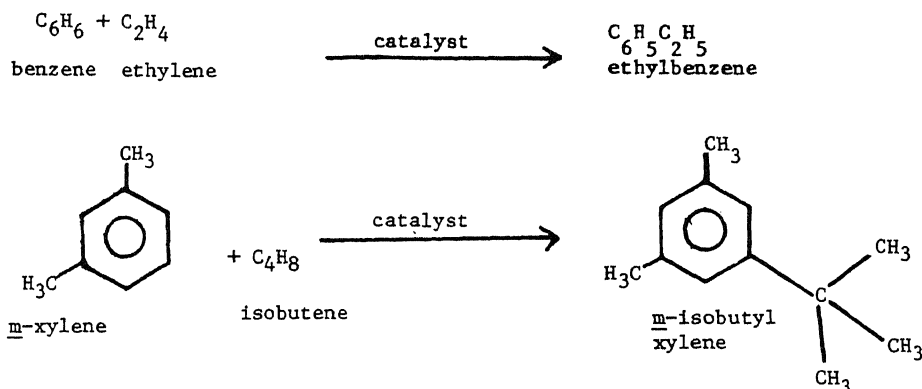
Condensation of the gaseous products from this thermal reaction leads to the production of a very stable polymer:



Errede and coworkers have conducted extensive research in this field (Errede and Knoll, 1962; Errede and Szwarc, 1958; Errede et al., 1960).

Badger and Spotswood (1960) reported that pyrolysis of ethylbenzene has produced aromatic hydrocarbons, some of which are suspected carcinogens (Table 2-6) (Christensen *et al.*, 1976). In their experiment, they passed ethylbenzene vapor with nitrogen through a silica tube filled with porcelain chips at 700°C.

Class 3 Reactions. The Friedel-Crafts reaction involves the alkylation of aromatic compounds, most commonly with aluminum chloride as catalyst, although many other metal halides have also been used to catalyze this reaction. The alkylations of most interest in this discussion are those involved in the formation of ethylbenzene and, to a more limited extent, those concerned with the production of higher molecular weight aromatics by the alkylation of xylenes.



Price (1946) has summarized more than 50 alkylation reactions of the xylenes and ethylbenzene involving various alkylating agents, catalysts, and operating conditions.

Reactions with Formaldehyde. *m*-Xylene, *o*-xylene, and *p*-xylene can be reacted separately in admixture with formaldehyde in the presence of an acid catalyst (generally sulfuric acid) to form resins. Of the three isomers, *m*-xylene is the most favored kinetically. The aromatic products of these reactions can further react with themselves or with other aromatic compounds or with more formaldehyde. Severe conditions may induce dehydration.

The products of these reactions are mixtures of polymers of hydrocarbons, ethers, acetals, and polyacetals. These polymers have relatively low molecular weights, probably not more than 1,000.

A number of complex reactions take place between the xylenes and formaldehyde. One such reaction results in the formation of a

TABLE 2-6. Compounds Identified in Tars Produced by the Pyrolysis of Ethylbenzene

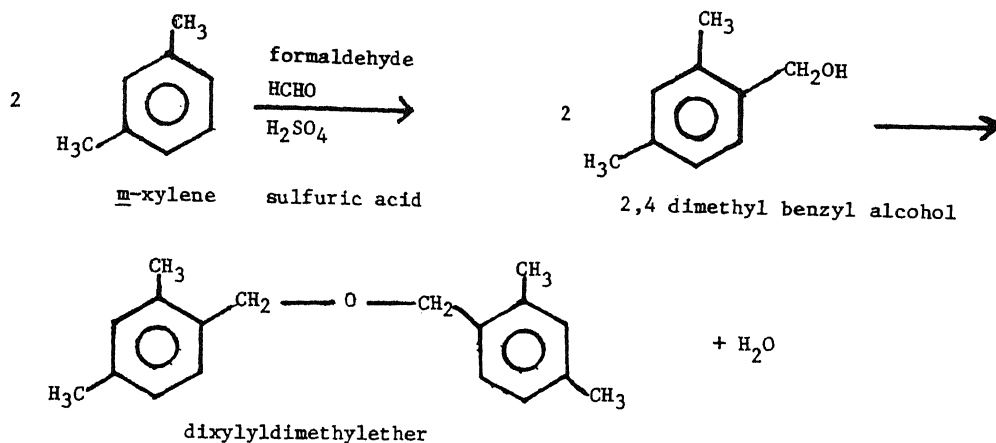
Compound	Weight, % of tar formed	Compound	Weight tar formed
Benaphthene	Trace	Ethylbenzene	0.7
Anthracene	0.88	Fluoranthene	0.3
Phenylanthracene ^b	0.012	Fluorene	0.5
1,2-Benzanthracene ^c	0.46	Indene	0.4
Benzo[a]pyrene ^c	34.8	1- and 2-Methylnaphthalene	0.0
4-Benzofluoranthene ^c	0.072	2-Methylstyrene ^b	0.1
1,11-Benzofluoranthene ^c	0.02	Naphthalene	4.5
1,12-Benzofluoranthene ^c	0.03	Perylene	0.0
2-Benzofluorene	0.42	Phenanthrene	14.3
3-Benzofluorene	0.79	Alkylphenanthrene ^b	0.2
1,2-Benzoperylene	0.03	9-Phenylanthracene	0.0
2-Benzopyrene ^c	0.05	2,3-(<u>o</u> -Phenylene)pyrene	0.0
4-Benzopyrene ^c	0.065	2-Phenylnaphthalene	0.4
Chrysene ^c	0.55	Pyrene	0.3
1-Methylchrysene	0.12	Stilbene	0.1
2,5,6-Dibenzanthracene ^c	0.054	Styrene	9.9
1-Benzyl	2.20	Toluene	21.6
2'-Binaphthyl	0.45	<u>p</u> -Xylene	0.1
1-Phenyl	3.11	Resins and losses	1.1

Data from Badger and Spotswood, 1960.

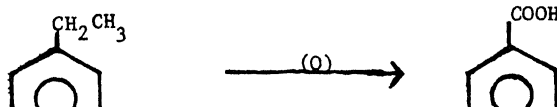
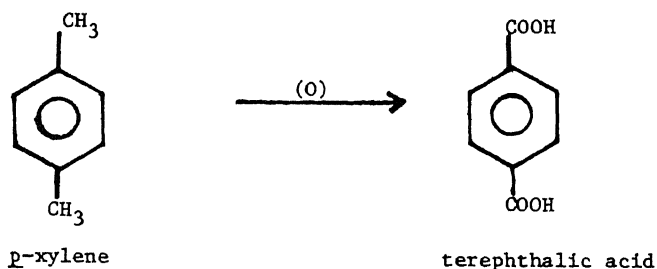
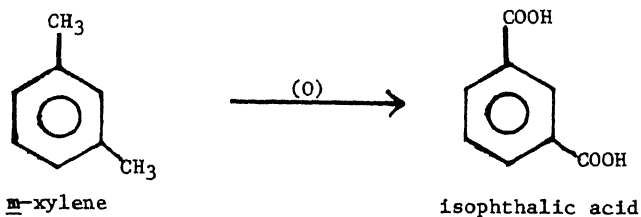
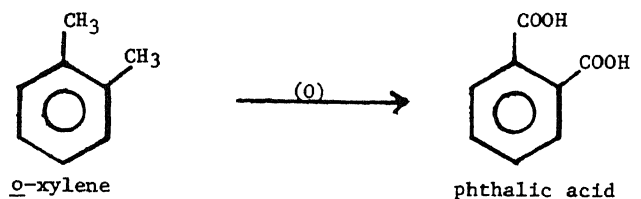
Structure doubtful, according to Badger and Spotswood (1960).

Suspected carcinogen (Christensen et al., 1976).

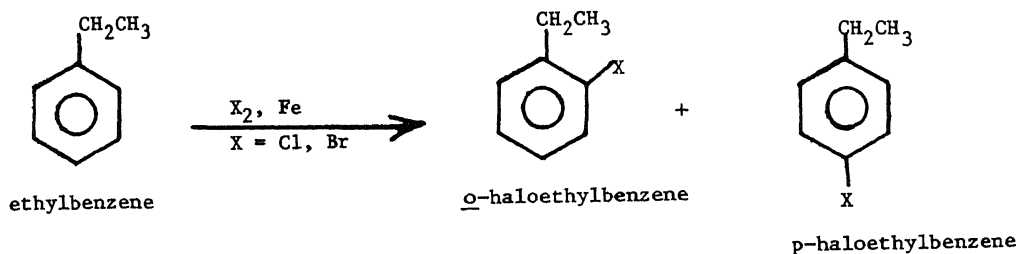
simple ether:



Oxidation. Although benzene and the alkanes are quite unreactive toward the usual oxidizing agents (potassium permanganate, potassium dichromate, etc.), the benzene ring favors oxidation of the aliphatic side chain, which is oxidized down to the ring. Only a carboxyl group (-COOH) remains to indicate the original position of the side chain. Potassium permanganate is generally used for this purpose, although potassium dichromate or dilute nitric acid is sometimes substituted.



Electrophilic Aromatic Substitution. Nitration of ethylbenzene results in the formation of o- and p-nitroethylbenzenes. Similarly, halogenation (chlorination or bromination) of ethylbenzene in the presence of ferric chloride or other halogens as catalysts gives o- and p-haloethylbenzenes:



The nuclear chlorination of various methylbenzenes in acetic acid solution, both with and without a catalyst, has been studied by Keefer and Andrews (1957). De La Mare and Robertson (1943) also examined the relative rates of nuclear chlorination. Condon (1948) has proposed a correlation of halogenation rates based on the data of De La Mare and Robertson (1943).

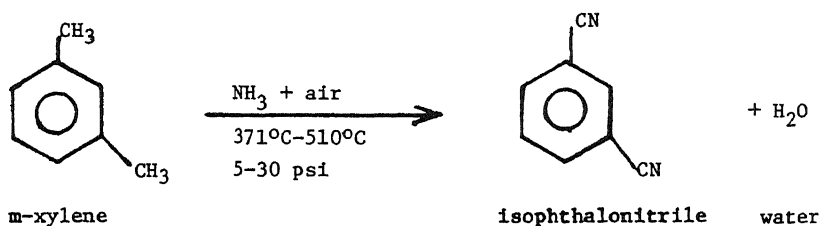
Extensive studies on the sulfonation of various methylbenzenes with sulfuric acid have been conducted by Kilpatrick et al. (1960) and Kilpatrick and Meyer (1961). Under their experimental conditions (15-18.6 M sulfuric acid at 25°C), the aromatics reacted completely to give the monosulfonic acids.

Electrophilic substitutions in xylene isomers are usually complicated by the presence of two electron-releasing methyl groups. Nuclear nitration studies directed specifically to the xylenes have been reported by Kobe and Levin (1950), Kobe and Brenneck (1954), and Kobe and Pritchett (1952).

Substitution in the Side Chain: Free Radical Halogenation. The chlorination and bromination of side chains differ significantly in their orientation and reactivity. The bromination of ethylbenzene yields 1-bromo-1-phenylethane as the only product, whereas the chlorination of ethylbenzene yields a mixture of 1-chloro-1-phenylethane (91%) and 2-chloro-1-phenylethane (9%). Halogenation in the side chain of xylene isomers can lead to substitutions in both of the methyl groups.

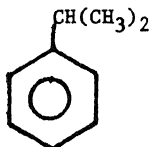
Reaction with Ammonia. Aromatic nitriles are produced directly from the corresponding alkyl benzenes through a vapor phase reaction termed "ammoxidation" (Hadley, 1961). This reaction takes place at high temperatures in the presence of a contact catalyst such as

adium pentoxide on alumina. Ammoxidation of m-xylene results in the production of isophthalonitrile:



isophthalonitrile is the main product (89%) of the ammoxidation of m-xylene. o-Xylene produces a mixture of phthalonitrile and phthalimide.

ISOPROPYLBENZENE (ISOPROPYLBENZENE)



cumene (isopropylbenzene)

Chemical Abstracts No. 98-82-8
(Chemical Abstracts Service, 1977)

Cumene (isopropylbenzene) is normally a liquid in the alkyl aromatic family of hydrocarbons, following toluene and ethylbenzene in the homologous chain. It is isomeric with several other compounds, such as n-propylbenzene, the ethyltoluenes, and the trimethylbenzenes. A synonym for this compound is 2-phenylpropane.

Physical Properties

A volatile liquid at atmospheric conditions, cumene is flammable at temperatures exceeding 35°C . It is clear when pure and has a characteristic aromatic odor. Care must be exercised when distilling cumene samples that have been exposed to air since cumene hydroperoxide may be present and may become concentrated. This contaminant is unstable and decomposes violently at approximately 140°C (LeRoux, 1955), which is lower than the boiling point of cumene. Some physical and thermodynamic properties of cumene are listed in Table 2-7.

TABLE 2-7. Physical and Thermodynamic Properties of Cumene

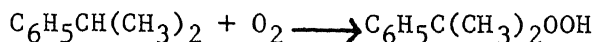
Property	Value	Property	Value
Molecular weight ^a	120.19	Flash point (tag closed-cup), °C ^c	35
Boiling point, 760 mm Hg, °C ^a	152.39	Vapor pressure, mm Hg: ^b	
Freezing point, °C ^a	-96.033	At 20°C	3.2
Density at 20°C, g/ml ^a	0.8618	At 38.29°C	10.0
Refractive index at 20°C ^a	1.49145	At 72.12°C	50.0
Vapor density (air = 1) ^b	4.13	Specific heat (liquid) at 25°C, cal/(g)(°C) ^a	0.369
Specific dispersion at 20°C	165.7	Critical Properties: ^c	
Viscosity at 20°C, cp ^c	0.791	Temperature, °C	351.4
Surface tension at 20°C, dyn/cm ^c	28.20	Pressure, atm	27.5
Solubility:		Density, g/ml	0.28
In distilled water	65.3 + 0.8		
at 25°C, mg/l ^d			
In seawater at			
25°C, mg/l ^d	42.5	Heat of vaporization at boiling point, cal/g ^c	74.6
In ethyl alcohol ^a	Soluble	Heat of formation at 25°C, kcal/mol ^c	-9.848
In ethyl ether ^a	Soluble	Entropy at 25°C, kcal/(mol)(°C) ^c	67.87
Flammable limits,			
% by volume in air ^c	0.88 - 6.50		

TABLE 2-7. Physical and Thermodynamic Properties of Cumene (cont'd)

Property	Value	Property
Free energy at 25°C, kcal/(mol)(°C)	29.708	Sources of spectral properties: Ultraviolet ^g Infrared ^h Nuclear magnetic resonance ^{i,j} Mass ^g
Partition coefficient (K_D) ^e in octanol and water ^f	4,571	
Conversion factors, in air at 25°C	1 ppm = 4.92 mg/m ³ 1 mg/m ³ = 0.203 ppm	
^a Weast, 1978	$K_D = \frac{\text{Concentration in octanol}}{\text{Concentration in water}}$	^h Pouchert, 1975
^b Glaser and Ruland, 1957		ⁱ Bhacca <u>et al.</u> , 1962
^c Rossini <u>et al.</u> , 1953		^j Pouchert and Campbell
		^f Leo <u>et al.</u> , 1971

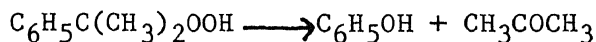
Properties

Reaction. The most important chemical reaction of cumene is its reaction with air to the unstable cumene hydroperoxide at elevated temperatures. This occurs during the manufacture of phenol:



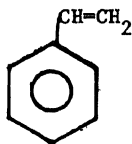
Cumene Cumene hydroperoxide
(isopropylbenzene)

The composition of the reaction mixture must be maintained outside the explosive range which, for cumene in dry air, ranges from approximately 1% to 8% by volume of hydrocarbon (Butler and Webb, 1955). The cumene hydroperoxide is cleaved or decomposed at approximately 100°C to form phenol and acetone (LeRoux, 1955):



cumene hydroperoxide phenol acetone

Reaction. Cumene can be further alkylated with propylene to form p-propylbenzenes. p-Diisopropylbenzene, which is fractionable from the other two isomers, can be oxidized to terephthalic acid. Thereby it can be used as a substitute raw material for p-xylene in the production of this acid.



Chemical Abstracts No. 100-42-5

(Chemical Abstracts Service, 1977)

Styrene is the common name for the simplest, but by far the most important, member of a series of unsaturated aromatic monomers. As discussed in Chapter 1, styrene is used extensively in the production of plastics and resins and in the styrene-butadiene rubber industry. Its derivatives include cinnamene, phenethylene, phenylethene, phenylethylene, styrene, styrol, styrole, styrolene, vinylbenzene, and vinylbenzol.

In the United States, polymer grade styrene usually conform to the following typical specifications: purity, 99.6% minimum; polymer, 10 mg/kg maximum; sulfur, 25 mg/kg maximum; chlorine, 5 mg/kg maximum; hydrogen peroxide, 100 mg/kg maximum; benzaldehyde, 200 mg/kg maximum; and tert-butyl catechol (as an inhibitor), 12 mg/kg. The product is free from suspended matter and is clear. specific gravity (d_{20}^{20}) is 0.9070-0.9080 (International Agency for Research on Cancer, 1979).

In Western Europe, styrene must meet the following specifications: purity, 99.6% minimum; polymer, 10 mg/kg maximum; sulfur, 30 mg/kg maximum; benzaldehyde, 0.02% (weight) maximum; hydrogen peroxide, 100 mg/kg maximum; and tert-butyl catechol, 10-15 mg/kg. Specifications for styrene produced in Japan are: purity, 99.5% minimum; specific gravity (d_{25}^{25}), 0.9038-0.9057; refractive index (n_D^{25}), 1.5435-1.5455; polymer content, 10 mg/kg maximum; and ethylbenzene present as an impurity. The product is colorless, clear, and contains no suspended matter (International Agency for Research on Cancer, 1979).

Physical Properties

The physical and thermodynamic properties of styrene monomer are listed in Table 2-8. Because styrene liquid and vapors are flammable, appropriate precautions should be taken to prevent their contact with open flames, hot spots, switches, etc. Equipment should be carefully grounded to avoid sparks from static electricity. Styrene does not possess sufficient vapor pressure at room temperature to form explosive mixtures with the atmosphere. However, only a slight rise in elevated temperature is necessary to raise the vapor concentration to potentially explosive levels (see flash point and fire point in Table 2-8).

Although oxygen tends to degrade styrene, some oxygen is necessary for the effective action of the inhibitor. Therefore, styrene should not be blanketed with an inert gas during storage. Properly inhibited and attended, styrene can be stored at ambient temperatures for long periods. However, in climates where temperatures exceeding 27°C are common, bulk quantities of monomer should be stored under refrigeration (Coulter et al., 1969). The chief impurities resulting from the oxidation of styrene are aldehydes (principally benzaldehyde and formaldehyde) and peroxides.

Copper or copper-bearing alloys should not contact styrene during processing or storage. Copper dissolved in the monomer can result in colored impurities and interfere with polymerization. Other materials, such as iron, steel, magnesium, and aluminum, do not affect the purity of styrene and can therefore be used satisfactorily (Coulter et al., 1969).

TABLE 2-8. Physical and Thermodynamic Properties of Styrene

Property	Value	Property	Value
Molecular weight ^a	104.14	Explosive limits in air, % ^b	1.1-
Boiling point at 760 mm Hg, °C ^a	145.2	Vapor pressure, mm Hg: ^b	
Freezing point, °C ^a	-30.60	At 20°C	5.5
Density at 20°C, g/ml ^a	0.9059	At 37°C	13.5
Refractive index at 25°C ^a	1.5439	Specific heat:	0.4
Viscosity at 20°C, cp ^b	0.763	At 20°C, liquid, cal/(g)(°C) ^b	
Surface tension at 20°C, dyn/cm ^b	80.86	At 25°C, vapor, cal/(g)(°C) ^b	0.28
Solubility at 25°C, %: ^b		Critical properties: ^b	
Monomer in water	0.032	Pressure, atm	37.6
Water in monomer	0.070	Temperature, °C	369.0
Flash point:		Volume, cm ³ /g	3.55
Tag open cup, °C ^b	34.44	Latent heat of vaporization	
Cleveland open cup, °C ^b	31.11	at 25°C, cal/g	102.40
Fire point:		Heat of combustion at 25°C,	
Tag open cup, °C ^b	34.44	gas, kcal/mol	1,018.8
Cleveland open cup, °C ^b	34.44	Heat of formation 25°C,	
Autoignition temperature, °C ^b	490	liquid, kcal/mol	35.22

Property	Value	Property
Heat of polymerization, kcal/mol ^b	17.8	Sources of spectral properties:
Dielectric coefficient (ϵ_D) ^c		Ultraviolet ^e
Partition coefficient in octanol and water ^d	891	Infrared ^f
Refractive indices		Nuclear magnetic resonance ^g
in air at 25°C	1 ppm = 4.26 mg/m ³	Raman ^e
	1 mg/m ³ = 0.235 ppm	Mass ^e

^dHansch and Leo, 1979
^eGrasselli and Ritchey, 1975b
^fPouchert, 1975
^gPouchert and Campbell, 1974

t, 1978
 ter et al., 1969
Concentration in octanol
Concentration in water

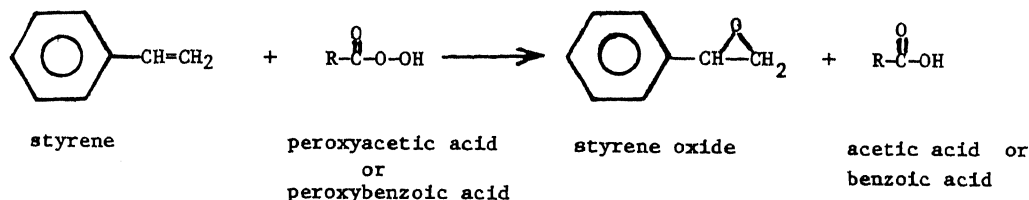
Chemical Properties

Polymerization. Polymerization or copolymerization of styrene is the only reaction that has commercial importance. Virtually all of the monomer manufactured is consumed by these processes. Styrene monomer can be polymerized by all the methods that are common in plastics technology. Mass, suspension, solution, and emulsion polymerization have been used in the manufacture of polystyrene and styrene copolymers, but processes relating to the first two methods account for most of the polymers manufactured today. Generally, a free-radical polymerization of the monomer is initiated thermally or with catalysts (Basdekis, 1964; Boundy and Boyer, 1952; Coulter et al., 1969; Elly et al., 1951; Ohlinger, 1955; Schildknecht, 1956).

Pure styrene also polymerizes slowly at room temperature and more rapidly under warmer conditions. This exothermic process could become self-accelerating. A runaway polymerization can create dangerously high temperatures and pressures within a storage vessel. The polymerization of the monomer can be retarded during storage by maintaining an inhibitor level of 10-15 ppm tert-butylcatechol (TBC) and by avoiding storage at excessively high temperatures (Coulter et al., 1969).

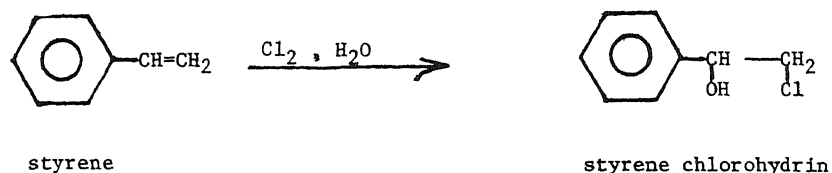
General-purpose polystyrene is a high molecular weight ($2-3 \times 10^5$), crystal-clear thermoplastic that is hard, rigid, and free of odor and taste. Normally, commercial polystyrenes are relatively pure polymers. The amounts of styrene, ethylbenzene, and styrene dimers and trimers that may be produced during the manufacture of polystyrene are reduced by devolatilization or by the use of catalysts for the mass and suspension processes, respectively. Polystyrenes with a low overall volatile content have high heat-deformation temperatures.

Epoxidation. Styrene undergoes epoxidation with peroxyacetic acid or peroxybenzoic acid to form styrene oxide:

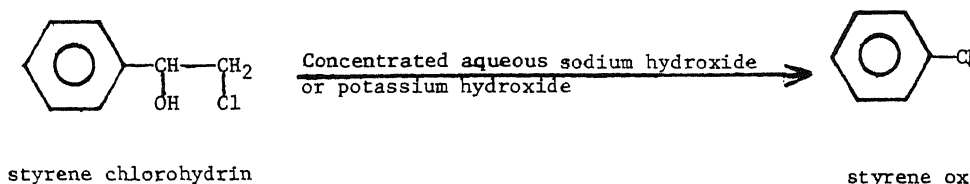


where R = CH₃- or C₆H₅-.

Addition. The addition of chlorine water across the vinyl group of the styrene leads to the production of styrene chlorohydrin



Styrene chlorohydrin is highly reactive. The addition of concentrated aqueous sodium or potassium hydroxide results in the production of styrene oxide:



Thermal Degradation of Polystyrene. The processing temperatures for polystyrene vary from 150°C to 300°C . In some operations, such as wirecutting, they may rise considerably higher. At these elevated temperatures the polymer undergoes some degradation, the products of which are emitted into the work environment. In a recent study by Pfaffli *et al.* (1978), pure polystyrene was treated in a laboratory oven at temperatures of 200°C , 350°C , and 500°C under an airflow of 0.7 liters/min. The thermal degradation products appearing in gas phase, vapor, and aerosol phases were collected and identified by gas chromatography/mass spectrometry. Thermogravimetric analysis indicated that the thermal degradation of the polymer began at 270°C in air and that it stopped at 425°C . The main groups of vaporized compounds generated were monoalkyl-substituted aromatic hydrocarbons and their oxidized products (Table 2-9), of which styrene monomer and benzene were the most abundant. Only trace amounts of carbon monoxide and aliphatic compounds (hydrocarbons, aldehydes, and acids) were present (Table 2-10). The resulting aerosol, which increased in quantity as the temperature rose, contained mainly fragments of the polymer.

LE 2-9. Aromatic Hydrocarbons and Their Oxidized Products Released from the
 Degradation of 100 mg of Polystyrene (mg, mean of five samples \pm SD)

Product	200°C	350°C	500°C
Aromatic hydrocarbons:			
Benzene	NA ^b	0.03 \pm 0.02	0.01 \pm 0.01
Toluene	NA	0.03 \pm 0.02	0.10 \pm 0.02
Ethylbenzene	Trace	0.04 \pm 0.01	0.01 \pm 0.01
Cumene	Trace	0.02 \pm 0.01	0.01 \pm 0.01
Styrene	Trace	5.22 \pm 0.83	5.84 \pm 1.94
Allylbenzene	NA	0.09 \pm 0.02	0.03 \pm 0.01
α -Styrene	NA	0.12 \pm 0.02	0.07 \pm 0.01
n-Propylbenzene	NA	<0.01	<0.01
Oxidized aromatic compounds:	NA		
Benzaldehyde		3.44 \pm 0.97	0.87 \pm 0.21
Cinnamaldehyde		<0.01	<0.01
Acetophenone		0.15 \pm 0.03	0.02 \pm 0.01
Benzyl alcohol		<0.01	<0.01
Styrene oxide		0.14 \pm 0.03	0.07 \pm 0.01
1-Phenylethanol		0.98 \pm 0.40	0.08 \pm 0.01
Benzoic acid		NA	0.03
Phenol		0.12 \pm 0.04	0.02 \pm 0.01

from Pfaffli et al., 1978.

Data not available.

TABLE 2-10. Aliphatic Compounds and Oxides Released From the Thermal Degradation of 100 mg of Polystyrene (mg, Mean of Three Samples)^a

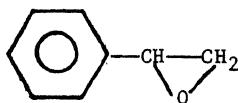
<u>Product</u>	<u>200°C</u>	<u>350°C</u>	<u>500°C</u>
Formaldehyde	0.006	0.17	0.1
Acrylaldehyde	Undetected	0.02	0.0
Formic acid	<0.01	<0.01	<0.0
Hydrocarbons	Undetected	<0.01	<0.0
Carbon monoxide	0.1 (7) ^b	0.4 (30) ^b	2.1

^aFrom Pfaffli et al., 1978.

^bppm (vol/vol) in outgoing air (12 liters).

chain (Table 2-11). At approximately 350°C, the most important thermal degradation products are styrene, benzaldehyde, acetophenone, and 1-phenylethanol. Their proportional molar concentrations in the mixture are: 1: 0.7: 0.5: 0.5, respectively, at 300°C.

STYRENE OXIDE



Chemical Abstracts No. 96-09-3
(Chemical Abstracts Service, 1977)

Styrene oxide is an important derivative of styrene monomer. Its synonyms include phenyloxirane, 1,2-epoxyethylbenzene, epoxy-styrene, α , β -epoxystyrene, phenethylene oxide, 1-phenyl-1,2-epoxyethane, phenylethylene oxide, 2-phenyloxirane, styrene epoxide, and styryl oxide.

In the United States, 98 mol % pure styrene oxide must conform to the following specifications: density, 1.0490-1.0515 (25/25°C); distillation range, 760 mm; boiling point of fraction between 5% and 95% by volume, 194.1°C \pm 3.0°C; water, 0.25% by weight maximum (Furukawa and Saegusa, 1967).

In Japan, styrene oxide is available commercially with a minimum purity of 98% and contains mono- and dichloroethylbenzene and unreacted styrene monomer as impurities. Additional Japanese specifications include: specific gravity, 1.0530-1.0560 (20/20°C); refractive index, 1.5330-1.5355 (20°C); boiling point, 194.1°C; and water, 0.1% maximum (International Agency for Research on Cancer, 1979).

Physical Properties

The physical properties of styrene oxide are listed in Table 2-12.

Chemical Properties

The reactions of styrene oxide are similar to those of the aliphatic epoxides such as ethylene oxide and propylene oxide. Alcohols add to styrene oxide in the presence of an acid or base

TABLE 2-11. Total Amount of Aerosol Collected at Different Temperatures
from the Thermal Degradation of 100 mg of Polystyrene

Temperature, °C	Amount, mg, mean \pm SD	Range	Number of Samples
200	0.1 \pm 0.1	0.05 - 0.3	1
350	18.9 \pm 6.7	10.7 - 26.7	1
500	26.5 \pm 0.9	25.2 - 27.4	1

^aFrom Pfaffli et al., 1978. The airflow was 0.7 liters/min. The exposure time was 15 min.

2-12. Physical Properties of Styrene Oxide

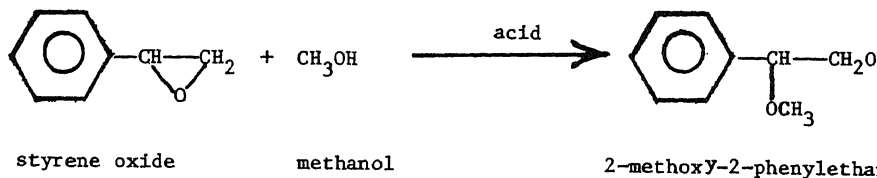
Property	Value	Property	Value
Molecular weight ^a	120.16	Solubility in other solvents: ^a	
Boiling point, 760 mm Hg, °C ^a	194.1	Acetone, benzene, carbon	Completely soluble
Freezing point, °C ^a	-36.8	tetrachloride, ethyl	in each
Specific gravity, 20/20 °C ^a	1.0540	ether, heptane,	
Vapor pressure, 20°C, mm Hg ^b	0.3	and methanol	
Viscosity, 20°C, cp ^b	1.99	Conversion factors (in air at	
Refractive index at 20°C ^a	1.5339	25°C)	1 ppm = 4.91 mg/m ³
Cloud point, °C ^b	80.0		1 mg/m ³ = 0.204 ppm
Stability at 20°C, by weight		Sources of spectral properties:	
Stability solution: ^b		Ultraviolet ^c	
Styrene oxide in water, %	0.30	Infrared ^d	
Styrene oxide in styrene oxide, %	0.50	Nuclear magnetic resonance ^e	
		Mass ^c	

^aPouchert, 1975

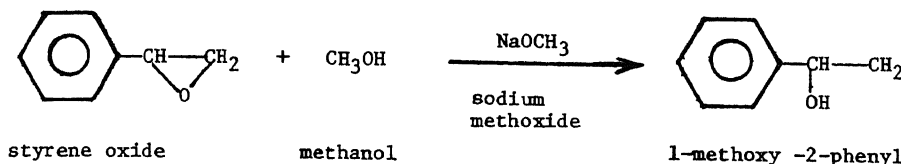
^bPouchert and Campbell, 1974

^celli and Ritchey, 1975b

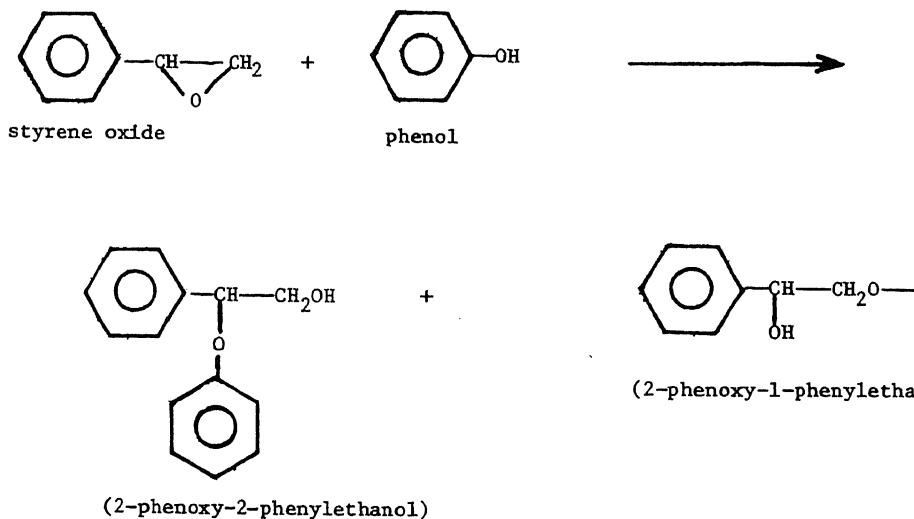
with methanol to produce a 90% yield of 2-methoxy-2-phenylethanol when catalyzed by acid (Reeve and Christoffel, 1950):



When sodium methoxide was used as a catalyst in the above reaction, the major product was the secondary alcohol (Kaelin)



The base-catalyzed condensation of phenol with styrene oxide produces a mixture of 2-phenoxy-2-phenylethanol and 2-phenoxy-1-phenylethanol:



reaction is conducted in an aqueous base or in nonaqueous, 2-phenoxy-2-phenylethanol is the major product. When excess is used as the solvent, 2-phenoxy-1-phenylethanol predominates (Williams, 1951).

reaction of styrene oxide with phenol at elevated temperatures in the formation of resinous condensation products (Lapkin, 1965).

ONS

yl derivatives of benzene, such as toluene, o-, m-, and p-, cumene (isopropylbenzene), styrene, and styrene oxide are volatile liquids that have high vapor pressures at room temperature. Although pyrolysis of toluene and ethylbenzene vapors in a silica tube produces low levels of some polycyclic aromatic hydrocarbons that are either known or suspected carcinogens, oxidation may not occur at ambient temperatures and pressures. Oxidation of cumene may pose an environmental health hazard as a product, cumene hydroperoxide, explodes violently to form acetone and acetophenone. At approximately 350°C, the thermal degradation of styrene produces styrene, benzaldehyde, acetophenone, and phenylethanol.

REFERENCES

- Adams, C. R. 1967. Oxidative dehydrogenation of alkyl benzenes with CaNiPO_4 and sulfur dioxide. U.S. Patent 3,299,155. Shell Chemical Co. [Chem. Abs. 66:55199q, 1967].
- American Petroleum Institute. 1966. Technical Data Book-Petroleum Refining. American Petroleum Institute, Division of Refining, New York. [loose leaf].
- Badger, G. M., and T. M. Spotswood. 1960. The formation of aromatic hydrocarbons at high temperatures. Part IX. The pyrolysis of toluene, ethylbenzene, propylbenzene, and butylbenzene. J. Chem. Soc.:4420-4427.
- Barnard, J. A., and B. M. Sankey. 1968. The slow combustion of isomeric xylenes. I. Meta- and para-xylene. Combust. Flame 12:345-352.
- Basdekis, C. H. 1964. Styrene polymers. Pp. 402-436 in W. M. Bassett, ed. Manufacture of Plastics, Volume I. Reinhold, New York.
- Becker, K., H. Blume, E. Hähner, and H. Grundmann. 1966. Versuche zur Isomerisierung technischer Xylolfractionen an Katalysatoren mit Alumosilicatträgern. [Tests on isomerizing technical xylene fractions to catalysts with aluminosilicate carriers]. Chem. Tech. (Leipzig) 18:455-459.
- Bethea, S. R., R. L. Heinrich, A. M. Souby, and L. T. Yule. 1955. Production of aromatics by hydrodealkylation. Ind. Eng. Chem. 50:1245-1252.
- Bhacca, N. S., L. F. Johnson, and J. Shoolery. 1962. High Resolution NMR Spectra Catalog. Varian Associates, Palo Alto, Calif.
- Boedeker, E. R., and W. E. Erner. 1954. Vapor phase catalytic isomerization of m-xylene. J. Am. Chem. Soc. 76:3591.
- Boundy, R. H., and R. F. Boyer, eds. 1952. Styrene: Its Polymers, Copolymers and Derivatives. Reinhold, New York. 1304 pp.
- Bradsher, C. K. 1977. Toluene. P. 682 in McGraw-Hill Encyclopedia of Science and Technology, 4th edition, Volume 13. McGraw-Hill Book Company, New York.
- Butler, J. C., and W. P. Webb. 1957. Upper explosive limits of organic vapors. Chem. Eng. Data Ser. 2:42-46.

- Chadwick, D. H., and E. E. Hardy. 1967. Isocyanates, organic. Pp. 45-64 in H. F. Mark, J. J. McKetta, Jr., and D. F. Othmer, eds. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd edition, Volume 12. Interscience, New York.
- Christensen, H. E., E. J. Fairchild, and R. J. Lewis, Sr., eds. 1976. Suspected Carcinogens, 2nd edition. A Subfile of the NIOSH Registry of Toxic Effects of Chemical Substances. HEW Publication No. (NIOSH) 77-149. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio.
- Cier, H. E. 1969. Toluene. Pp. 527-565 in H. F. Mark, J. J. McKetta, Jr., and D. F. Othmer, eds. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd edition, Volume 20. Interscience, New York.
- Cier, H. E. 1970. Xylenes and ethylbenzene. Pp. 467-507 in H. F. Mark, J. J. McKetta, Jr., and D. F. Othmer, eds. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd edition, Volume 22. Interscience, New York.
- Condon, F. E. 1948. Correlation of rates of halogenation of methylbenzenes. J. Am. Chem. Soc. 70:1963-1964.
- Coulter, K. E., H. Kehde, and B. F. Hiscock. 1969. Styrene. Pp. 55-85 in H. F. Mark, J. J. McKetta, Jr., and D. F. Othmer, eds. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd edition, Volume 19. Interscience, New York.
- De La Mare, P. B. D., and P. W. Robertson. 1943. The kinetics of aromatic hydrocarbons. Part II. The chlorination of hydrocarbons. J. Chem. Soc.:279-281.
- Elly, J., R. N. Haward, and W. Simpson. 1951. Some factors affecting the useful rates of reaction in the industrial polymerization of styrene. J. Appl. Chem. 1:347-353.
- Errede, L. A., and N. Knoll. 1962. The chemistry of xylylenes. XIV. The moldability and thermal stability of poly (p-xylylene) and related polymers. J. Polymer Sci. 60:33-42.
- Errede, L. A., and M. Szwarc. 1958. Chemistry of p-xylylene its analogs, and polymers. Quart. Revs. (London) 12:301-320. [Chem. Abs. 53:8024i, 1959.]
- Errede, L. A., R. S. Gregorian, and J. M. Hoyt. 1960. The chemistry of xylylenes. VI. The polymerization of p-xylylene. J. Am. Chem. Soc. 82:5218-5223.

- Furukawa, J., and T. Saegusa. 1967. 1,2-Epoxy polymers. Pp. 195 in H. F. Mark, N. G. Gaylord, and N. M. Bikales, eds. *Encyclopedia of Polymer Science and Technology: Plastics, Resins, Fibers*, Volume 6. Interscience, New York.
- Gait, A. J. 1967. *Heavy Organic Chemicals*. Pergamon, Oxford, 249 pp.
- Glaser, F., and H. Rüland. 1957. Vapor pressure curves and critical data of some technically important organic substances. *Chem. Tech.* 29:772-775. [Chem. Abs. 52:7115f, 1958.]
- Grasselli, J. G., and W. M. Richey, eds. 1975a. *CRC Atlas of Spectroscopic Data and Physical Constants for Organic Compounds*, 2nd edition, Volume II. CRC Press, Inc., Cleveland, Ohio. 644 pp.
- Grasselli, J. G., and W. M. Richey, eds. 1975b. *CRC Atlas of Spectroscopic Data and Physical Constants for Organic Compounds*, 2nd edition, Volume IV. CRC Press, Inc., Cleveland, Ohio. 538 pp.
- Guss, C. O., and H. R. Williams. 1951. The effect of solvent and temperature on the base-catalyzed reaction of styrene oxide with phenol. *J. Org. Chem.* 16:1809-1816.
- Hadley, D. J. 1961. The ammoxidation route to nitriles. *Chem. Ind. (London)* 8:238-243.
- Hansch, C., and A. Leo. 1979. *Substituent Constants for Correlation Analysis in Chemistry and Biology*. Wiley, New York. 218 pp.
- Hanson, C., and H. A. M. Ismail. 1975. Solubility and distribution data for benzene and toluene between aqueous and organic phases. *J. Appl. Chem. Biotechnol.* 25:319-325.
- Hoff, M. C. 1958. Interaction of xylenes with ethylbenzene. *J. Am. Chem. Soc.* 80:6046-6049.
- International Agency for Research on Cancer. 1979. Styrene, polystyrene and styrene-butadiene copolymers. Pp. 231-274 in *Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Volume 19. International Agency for Research on Cancer, Lyon, France.
- Kaelin, A. 1947. Synthese des Sauerstoffisologen des Adrenalin und der isomeren Verbindung. *Helv. Chim. Acta* 30:2132-2141.
- Keefer, R. M., and L. J. Andrews. 1957. The kinetics of aromatic hydrocarbon chlorination in acetic acid. The use of zinc chloride as a catalyst and of iodobenzene dichloride as a halogen source. *J. Am. Chem. Soc.* 79:4348-4353.

- Kelley, K. K. 1929. The heat capacity of toluene from 14°K to 298°K. The entropy and the free energy of formation. J. Am. Chem. Soc. 51:2738-2741.
- Kilpatrick, M., and M. W. Meyer. 1961. The kinetics of the reactions of aromatic hydrocarbons in sulfuric acid. II. Toluene, the xylenes, pseudocumene and hemimellitene. J. Phys. Chem. 65:530-532.
- Kilpatrick, M., M. W. Meyer, and M. L. Kilpatrick. 1960. The kinetics of the reactions of aromatic hydrocarbons in sulfuric acid. I. Benzene. J. Phys. Chem. 64:1433-1435.
- Kobe, K. A., and H. M. Brennecke. 1954. Mononitration of m-xylene. Ind. Eng. Chem. 46:728-732.
- Kobe, K. A., and H. Levin. 1950. Mononitration of p-xylene. Ind. Eng. Chem. 42:352-356.
- Kobe, K. A., and P. W. Pritchett. 1952. Mononitration of o-xylene. Ind. Eng. Chem. 44:1398-1401.
- Lapkin, M. 1965. Epoxides. Pp. 263-293 in H. F. Mark, J. J. McKetta, Jr., and D. F. Othmer, eds. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd edition, Volume 8. Interscience, New York.
- Leo, A., C. Hansch, and D. Elkins. 1971. Partition coefficients and their uses. Chem. Rev. 71:525-616.
- LeRoux, A. 1955. Explosive tendency of cumene hydroperoxide. Mém. Poudres 37:49-58. [Chem. Abs. 51:718f, 1957.]
- Lien, A. P., and D. A. McCaulay. 1953. Disproportionation of alkylbenzenes. I. Product distribution and rate studies. J. Am. Chem. Soc. 75:2407-2410.
- McCaulay, D. A., and A. P. Lien. 1952. Isomerization of the methylbenzenes. J. Am. Chem. Soc. 74:6246-6250.
- McCauley, D. A., and A. P. Lien. 1957. Disproportionation of alkylbenzenes. IV. Ethylbenzene and diethylbenzene. J. Am. Chem. Soc. 79:5953-5955.
- McCauley, D. A., M. C. Hoff, N. Stein, A. S. Couper, and A. P. Lien. 1957. Disproportionation of alkylbenzenes. V. Ethylbenzene interaction with xylenes. J. Am. Chem. Soc. 79:5808-5809.

- Nelson, K. L. 1955. Friedel-Crafts reactions. Ind. Eng. Chem. 47:1926-1943.
- Norris, J. F., and G. T. Vaala. 1939. The arrangement of the xy by aluminum chloride. J. Am. Chem. Soc. 61:2131-2134.
- Ohlinger, H. 1955. Polystyrol. Erster Teil. Herstellungsverfa und Eigenschaften der Produkte. Springer-Verlag, Berlin, Fe Republic of Germany. 155 pp.
- Olson, D. H. 1968. Styrene production by dehydrogenation of eth benzene. U.S. Patent 3,406,219. Marathon Oil Co. [Chem. 70:11322c, 1969.]
- Pfaffli, P., A. Zitting, and H. Vainio. 1978. Thermal degradat products of homopolymer polystyrene in air. Scand. J. Work Environ. 4(Suppl. 2):22-27.
- Pitts, P. M., Jr., J. E. Connor, Jr., and L. N. Leum. 1955. Is merization of alkyl aromatic hydrocarbons. Ind. Eng. Chem. 47:770-773.
- Pitzer, K. S., and D. W. Scott. 1943. The thermodynamics and molecular structure of benzene and its methyl derivatives. J. Am. Chem. Soc. 65:803-829.
- Pouchert, C. J. 1975. The Aldrich Library of Infrared Spectra, 2nd edition. Aldrich Chemical Co., Inc., Milwaukee, Wisc. 1576 pp.
- Pouchert, C. J., and J. R. Campbell. 1974. The Aldrich Library of NMR Spectra, Volume IV. Aldrich Chemical Co., Inc., Milwaukee, Wisc. 167 pp.
- Price, C. C. 1946. The alkylation of aromatic compounds by the Friedel-Crafts method. Pp. 1-82 in R. Adams, W. E. Bachman, L. F. Fieser, J. R. Johnson, and H. R. Snyder, eds. Organic Reactions, Volume 3. Wiley, New York.
- Reeve, W., and I. Christoffel. 1950. The reaction of styrene o with methanol. J. Am. Chem. Soc. 72:1480-1483.
- Rossini, F. D., K. S. Pitzer, R. L. Arnett, R. M. Braun, and G. Pimentel. 1953. Selected Values of Physical and Thermodyn Properties of Hydrocarbons and Related Compounds; Comprisin the Tables of the American Petroleum Institute Research Pro 44 extant as of December 31, 1952. Carnegie Press, Pittsbu Penna. 1050 pp.

- Sanders, H. J., H. F. Keag, and H. S. McCullough. 1953. Acetophenone. A staff-industry collaborative report. Ind. Eng. Chem. 45:2-14.
- Sax, N. I., and P. B. Sax. 1974. Encyclopedia Index. Pp. 577-683 in N. I. Sax, ed. Industrial Pollution. Van Nostrand Reinhold, New York.
- Schildknecht, C. E., ed. 1956. Polymer Processes. Interscience, New York.
- Silsby, R. I., and E. W. Sawyer. 1956. The dealkylation of alkyl aromatic hydrocarbons. I. The kinetics and mechanism of toluene decomposition in the presence of hydrogen. J. Appl. Chem. 6:347-356.
- Sutton, C., and J. A. Calder. 1975. Solubility of alkylbenzenes in distilled water and seawater at 25.0°C. J. Chem. Eng. Data 20:320-322.
- Tsuchiya, A., A. Hashimoto, H. Tominaga, and S. Masamune. 1959. A kinetic study of the hydrogenolytic dealkylation of toluene with high-pressure flow reactor. Bull. Jpn. Pet. Inst. 1:73-77. [Chem. Abs. 53:22829h, 1959.]
- Tsuchiya, A., A. Hashimoto, H. Tominaga, and S. Masamune. 1960. Dealkylation rates of xylene isomers in the presence of high-pressure hydrogen. Bull. Jpn. Pet. Inst. 2:85-93. [Chem. Abs. 55:964c, 1961.]
- U.S. Department of Health, Education, and Welfare. 1975. Criteria for a Recommended Standard... Occupational Exposure to Xylene. HEW Publication No. (NIOSH) 75-168. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio. 101 pp.
- Weast, R. C., ed. 1978. CRC Handbook of Chemistry and Physics. A Ready-Reference Book of Chemical and Physical Data, 59th edition. CRC Press, Inc., West Palm Beach, Fla. [2500] pp.

TECHNIQUES FOR MEASUREMENT

A number of techniques are used for sampling and analyzing the alkyl benzenes in different media. Samples may be collected in plastic bags, the vapors may be adsorbed onto silica gel or activated charcoal, or, in some cases, the measurements can be made directly. The methods currently used for analyzing the alkyl benzenes in air, water, and biological tissues include colorimetry, ultraviolet spectrophotometry, infrared analysis, gas chromatography, gas-liquid chromatography, thin-layer chromatography, and gas chromatography-mass spectrometry.

This chapter describes the application of various sampling and analytic techniques for specific alkyl benzenes and comments on their relative sensitivities.

ATMOSPHERIC ALKYL BENZENESSampling

Toluene. Toluene is collected from the air in several ways including plastic bags (Smith and Pierce, 1970), absorption in scrubbers by nitrating solution (Baernstein, 1943; Yant et al., 1936) or organic solvents (Dambrauskas and Cook, 1963; Maffett et al., 1956), and adsorption on silica gel (Whitman and Johnston, 1964) or activated charcoal (Burnett, 1976; Kupel and White, 1971; Reid and Halpin, 1968; White et al., 1970).

Adsorption on activated charcoal is the most efficient and easiest to use (National Institute for Occupational Safety and Health, 1977d; Reid and Halpin, 1968; White et al., 1970). Methods involving absorbing liquids require more extensive field sampling equipment. Moreover, it is inconvenient to obtain individual breathing-zone samples, especially when two or more scrubbers must be connected in series to assure a high collection efficiency (Pagnotto and Lieberman, 1967; Reid and Halpin, 1968). Activated charcoal is also preferable to silica gel because aromatic hydrocarbons such as toluene are easily displaced from silica gel by water vapor, resulting in possible losses of the sample in humid atmospheres (Whitman and Johnston, 1964). The design of activated charcoal tubes for sampling toluene vapor in industrial atmospheres and the conditions of sampling and desorption have been defined by White et al. (1970). They reported average desorption efficiencies of 100% (range, 97%-102%) and 95% (range, 93%-96%) for 100 ppm concentrations of toluene sampled alone and in the presence of six other organic vapors, respectively.

Xylenes. Xylenes can be measured directly in the field with a calibrated combustible gas indicator (Gerarde, 1963; Olishifski and

McElroy, 1971), but this method is not specific because it is subject to interference by other organic compounds. Detector tubes offer a rapid, simple procedure, but they depend upon an estimation of the length of a stain produced in the tube or upon the intensity of color produced. Consequently, these tubes are not particularly accurate. They are also nonspecific since other aromatic hydrocarbons may produce colors as well (American Conference of Governmental Industrial Hygienists, 1972; Hay, 1964; Kusnetz et al., 1960).

Collection in a bubbler containing sulfuric acid and formaldehyde has also been proposed, but this method is little more than semiquantitative (Hanson et al., 1965). Dambrauskas and Cook (1963) have described collection in a bubbler containing methanol and subsequent measurement by ultraviolet spectrophotometry. This method is disadvantageous because it requires that the sampling unit be placed in dry ice to prevent evaporation. Moreover, sampling of breathing zone exposures is more difficult with devices that contain liquids.

Silica gel has been used by a number of investigators to collect xylene vapor for laboratory analysis (Campbell and Ide, 1966; Croghan and Kaminsky, 1963; Feldstein et al., 1967). In the presence of water vapor, however, there may be considerable loss. Whitman and Johnston (1964) reported that this disadvantage could be overcome by the use of a molecular sieve prefilter.

Plastic bags have also been used to collect xylene and other organic vapors (Apol et al., 1966; Smith and Pierce, 1970; Vanderhoff and VanFarowe, 1965). To use this method effectively, one must pre-determine possible losses through reaction of the sample with the type of plastic that comprises the bag.

Adsorption of xylene vapor on activated charcoal has been studied by the National Institute for Occupational Safety and Health (NIOSH) (1977e), Otterson and Guy (1964), Reid and Halpin (1968), and White et al. (1970). This is the preferred method for sampling xylene since the compound is not displaced by water vapor, as it is when silica gel is used. Furthermore, it is simpler and more convenient than procedures involving plastic bags or bubblers. White et al. (1970) have described activated charcoal tubes that are suitable for sampling occupational exposures to xylene. They reported average desorption efficiencies (percent xylene recovered from the charcoal) of 94% (range 91%-96%) for 100 ppm concentrations of xylene sampled alone and 98% (range 97%-100%) in the presence of six other organic vapors. These tubes are now commercially available.

Ethylbenzene and Cumene (Isopropylbenzene). Adsorption on activated charcoal is also the preferred method of sampling for ethylbenzene and cumene (National Institute for Occupational Safety and Health, 1977a, b, c). In this procedure, a known volume of a

is drawn through a charcoal tube to trap the organic vapors. The charcoal in the tube is then transferred to a small, stoppered container, and the sample is desorbed with carbon disulfide.

Styrene. Styrene can be collected on charcoal, extracted with carbon disulfide, and analyzed by gas chromatography with an 85% to 90% average efficiency in concentrations ranging from 210 to 840 mg/m³ (Burnett, 1976). Dimethylformamide has been used for the extraction procedure with similar efficiency (Kalliokoski and Pfäffli, 1975). Atmospheric concentrations of styrene ranging from 1.7 µg/m³ to 1.7 mg/m³ can be determined by collection on charcoal, heat desorption, and gas chromatography (Parkes et al., 1976).

Analysis: General Methods

Toluene. Methods for analyzing toluene include colorimetry, which involves nitration followed by reaction with various ketones (Baernstein, 1943; Yant et al., 1936), ultraviolet spectrophotometry (Dambrauskas and Cook, 1963; Maffett et al., 1956), direct estimation by colorimetric indicator tubes (Hubbard and Silverman, 1950; Kol'kovsky, 1967), and gas chromatography (Anger et al., 1973; National Institute for Occupational Safety and Health, 1977d; Rappaport and Fraser, 1976; Reid and Halpin, 1968; Whitman and Johnston, 1964; Williams, 1965).

Xylenes. Methods for analyzing samples containing xylenes include colorimetry (Hanson et al., 1965), infrared analysis (Feldstein et al., 1967), and ultraviolet spectrophotometry (Campbell and Ide, 1966; Dambrauskas and Cook, 1963; Maffett et al., 1956). Gas chromatography is the method of choice for analyzing organic solvents.

Ethylbenzene. In general, the analytical procedures described for xylenes are applicable to ethylbenzene. Ethylbenzene probably comprises approximately 10% of the total aromatic compounds detected in the air and roughly 1% of the total carbon compounds.

Cumene. Methods for determining cumene vapor in the air are similar to those described for xylenes. The most common method of analysis is gas-liquid chromatography. However, absorption is frequently measured in the infrared region for positive identification of cumene. Wavelengths of 14.4, 13.15, and 9.54 µm are used where absorption maxima occur (Ward, 1965).

Styrene. The International Union of Pure and Applied Chemistry has adopted a colorimetric method for determining styrene in air. The limit of detection for this method is 840 mg/m³ (Gage et al., 1962). Ultraviolet spectrophotometric methods with absorptions of 247 or 245 nm have been used to determine styrene in polymers and copolymers with

a limit of detection ranging from 0.01 to 0.02 mg/liter (Petrova et al., 1974) and styrene in biological fluids of laboratory animals with a limit of detection of 1,000 ng per sample (Murav'eva and Smolyar, 1974).

Residual styrene in commercial styrene-butadiene latexes at concentrations ranging from 0.6 to 12.4 wt % has been determined by Raman spectral analysis. The results of these analyses are similar within 0.25% to those obtained by high-pressure liquid chromatography (Wancheck and Wolfram, 1976).

Thin-layer chromatography has been used to determine styrene as a residual starting material in the laboratory preparation of synthomol and levomycetin. Dolgoplov and Lishcheta (1971) reported the limit of detection for this method to be 100 µg per sample. Styrene has also been determined in benzene extracts of nine samples of styrene-acrylonitrile copolymers by titrimetry using bromination (Roy, 1977).

Styrene oxide can be determined volumetrically in epoxide-glycol mixtures (Swan, 1954). Microgram quantities of the compound have been analyzed by thin-layer chromatography (Dolgoplov and Lishcheta, 1971; Kulicka et al., 1967). At the nanomole level, it has been determined by indirect spectrophotometry (Mishmash and Meloan, 1972).

Analysis: Gas Chromatography

The colorimetric and direct spectrophotometric methods are subject to interferences from a wide variety of compounds. Removal of these interferences is tedious and, in many cases, incomplete. Gas chromatography offers the greatest specificity and sensitivity of the numerous methods available for analysis of alkyl benzenes. The small quantities of these hydrocarbons that generally occur in the environment are usually measured by gas chromatography with hydrogen flame ionization detection, either directly or as preconcentrated samples. Excellent original articles and reviews have been written by Andreatch and Feinland (1960), Balint et al. (1974), Bruderreck et al. (1964), Burchfield and Storrs (1962), Graziani et al. (1970), Halász and Schneider (1962), Khubulava et al. (1973), Kupel and White (1971), NIOSH (1977a-e), Pilar and Graydon (1973), Reid and Halpin (1968), Siegel et al. (1974), Švob and Deur-Siftar (1974), White et al. (1970), Whitman and Johnston (1964), and Wronski et al. (1972).

Ambient Measurements

Procedures for gas chromatographic measurements of alkyl benzenes at ambient levels in the environment have been described

by Altshuller et al. (1971), Leonard et al. (1976), and Lonneman et al. (1968). Typically, a 300' x 1/8" O.D. copper open tubular column coated with m-bis(M-phenoxyphenoxy)benzene and Apiezon grease is used with a flame ionization detector. The helium flow rate ranges from 46 to 66 ml/min; the column temperature ranges from 70°C to 74°C; the hydrogen pressure is 14 psi; and the air pressure is 50 psi.

To determine trace organic vapor pollutants in ambient atmospheres, the vapors are collected in Tenax gas chromatography cartridges containing 2,6-diphenyl-p-phenyleneoxide polymer. This is followed by thermal desorption and further analysis by a capillary gas-liquid chromatograph with a flame ionization detector coupled to a mass spectrometer (Pellizzari et al., 1976). Typically, 200' OV-17 or 200-400' OV-101 support coated open tubular (SCOT) capillary columns are programmed from 20°C to 220°C at 4°C/min. The carrier gas stream enters the mass spectrometer through a single-stage glass jet separator and quartz microprobe inlet, which are maintained at 200°C. An on-line computer records data on magnetic tape and generates normalized mass spectra and mass fragmentograms.

Specific references for the gas chromatographic measurements of ambient concentrations of some alkyl benzenes (range of sensitivity: 0.05-25 ppb) are: toluene (Altwickler et al., 1977; Leonard et al., 1976; Pellizzari, 1979; Russell, 1977; Singh et al., 1979; Stephens, 1973), ethylbenzene (Altshuller and Bellar, 1963; Altshuller et al., 1971; Lonneman et al., 1968; Neligan et al., 1965; Pellizzari, 1979; Russell, 1977; Singh et al., 1979), xylene (Altshuller et al., 1971; Lonneman et al., 1968; Pellizzari, 1979; Russell, 1977; Singh et al., 1979), and cumene (Lonneman et al., 1968; Neligan et al., 1965).

Gas chromatography-mass spectrometry has been used to identify 0.42 mg/m³ concentrations of styrene in volatile gases released during rubber vulcanization (Rappaport, 1975; Rappaport and Fraser, 1976). Hoshika (1977) used gas chromatography with electron-capture detection on one sample of urban air to determine styrene as its dibromide derivative at a concentration of 0.8 µg/m³. The limit of detection was approximately 0.01 ng per sample, approximately 500 times more sensitive than flame-ionization detection (Hoshika, 1977).

Styrene has been detected in the ambient air in concentrations of 0.84 µg/m³ in Nagoya, Japan (Hoshika, 1977); 0.4 µg/m³ (maximum 2.9 µg/m³) in Delft, The Netherlands (Bos et al., 1977); in the streets of Leningrad, USSR (Ioffe et al., 1977); and in Alabama in the city of Tuscaloosa and in a national forest (Holzer et al., 1977).

Occupational Measurements

NIOSH (1977a-e) recommends the following gas chromatographic procedure for the analysis of toluene in air:

Principle of the Method. A known volume of air is drawn through a charcoal tube to trap the organic vapors. The charcoal in the tube is transferred to a small, stoppered container, and the sample is desorbed with carbon disulfide. An aliquot of the desorbed sample is injected into a gas chromatograph equipped with a flame ionization detector and column. The area of the resulting peak is determined and compared with areas obtained for standards. Typical operating conditions for gas chromatography are listed in Table 3.

Interferences. When the amount of water in the air is so great that condensation occurs in the tube, organic vapors will not be trapped efficiently. When interfering compounds are known or thought to be present in the air, the containers of collected samples should be labelled with such information, including the suspected identities of the compounds.

Residual styrene in styrene polymers can be determined by gas chromatography by a headspace method. Using this method, Steichen (1976) obtained a limit of detection of 1 mg/kg; Kleshcheva et al. (1971) obtained a limit of detection of 10 mg/kg; and Zizin et al. (1974), after extraction in water vapor and concentration in a suitable solvent, obtained a limit of detection of 1 mg/kg. Swiatecki and Zowall (1975) were able to detect concentrations of 0.03% to 1.0% by the same method. Gas chromatography can also be used to determine styrene migrating from medical polymers to water (Markel and Semenenko, 1976) and from packaging materials to foods (Davies, 1974).

In combination with flame-ionization detection and mass spectrometry, gas chromatography has been used to study factors that affect the transfer of styrene from polystyrene containers to milk, which increases with temperature and storage time (Yamashita et al., 1974). This same method has been used with a limit of detection of 50 µg to determine styrene and related hydrocarbons in the subcutaneous fat of workers in a styrene polymerization plant (Wolff et al., 1974).

The quantity of styrene oxide produced by the action of styrene oxidase on styrene can be determined by hydrating the compound to styrene glycol followed by esterification with pentafluorobenzoyl chloride to a highly sensitive derivative analyzed by gas chromatography-electron capture detection. The limit of detection with this method is 0.01 ng/injection (van Bogaert et al., 1978).

TABLE 3-1. Typical Operating Conditions for the Gas Chromatographic Analysis of Toluene, Ethylbenzene, Xylenes, Cumene, and Styrene in Air^a

Equipment and Operating Conditions		Toluene	Ethylbenzene	Xylenes	Cumene	Styrene
Column:						
Dimension		3'x1/8" O.D.	10'x1/8" O.D.	3'x1/8" O.D.	10'x1/8" O.D.	10'x1/8" O.D.
Material		Stainless steel	Stainless steel	Stainless steel	Stainless steel	Stainless steel
Packing material		Porapak Q	10% FFAP ^b on acid-washed DMCS ^c	Porapak Q	10% FFAP ^b on acid-washed DMCS ^c	10% FFAP ^b on acid-washed DMCS ^c
Detector		FID ^d	Chromosorb W FID ^d	FID ^d	Chromosorb W FID ^d	Chromosorb W FID ^d
Temperature, °C:						
Column		155	85	180	99	109
Injector		200	195	215	195	195
Detector		265	250	275	255	255
Gas flow, ml/min:						
Nitrogen		50	50	50	50	50
Hydrogen		65	65	65	65	65
Airflow to detector		500	500	500	500	500
Range and sensitivity,						
mg/cm ³		555-2,220	222-484	210-870	120-480	426-1,710
Precision, CV _r		0.052	0.041	0.060	0.059	0.057

^aData collected from NIOSH, 1977a-e.

^bFFAP-Free Fatty Acid Packing.

^cDMCS-Dimethyldichlorosilane.

^dFID-Flame Ionization Detector.

ALKYL BENZENES IN WATER

Analysis

Many techniques used to analyze alkyl benzenes in water are similar to those used to analyze air. Again, gas chromatography with a flame ionization detector is the method of choice for determining the concentration in water. Although direct aqueous injection is occasionally used in such analyses (McKinney et al., 1976), it is usually necessary to concentrate the sample before by carbon adsorption, solvent extraction, freeze drying, steam distillation, reverse osmosis, inert gas stripping, and resin sorption (Garrison, 1977; Keith, 1976; Kopfler et al., 1975; Sauer et al.

Toluene. Seventeen U.S. drinking water supplies have been monitored (mostly by gas chromatography followed by mass spectrometry) to determine if they were contaminated with toluene. Most of the monitoring permitted only a determination of the presence of toluene, not the quantity. Toluene was detected in 14 of the 17 supplies in concentrations ranging from trace to 1 ng/liter (Bertsch et al., 1975; Coleman et al., 1976; Dowty et al., 1975; Keith et al., 1976; Kleopfer, 1976; Kopfler et al., 1975; Scheiman et al., 1974; Suta and Radziul, 1976).

In a nationwide survey sponsored by the U.S. Environmental Protection Agency (EPA), toluene was detected in drinking water at 14 times (Shackelford and Keith, 1976). The exact locations and concentrations were not reported. Toluene was also detected in the finished drinking water of one of 111 communities during a second nationwide survey sponsored by the EPA. In a subsequent phase of this survey, toluene was found in one raw water sample and in three finished waters of the 11 supplies surveyed. In a report prepared for the EPA, Suta (1979) stated that the concentrations of toluene ranged from 0.5 to 19 ng/liter.

Xylenes. Xylene isomers were detected in the drinking water of five U.S. cities by gas chromatography, but concentrations were not quantified. These studies were conducted in Tuscaloosa, Ala. (Bertsch et al., 1975), Houston, Tex. (Bertsch et al., 1975), Philadelphia, Pa. (Suffet and Radziul, 1976), New Orleans, La. (Dowty et al., 1975; Keith et al., 1976), and Washington, D.C. (Saunders et al., 1975). Dowty et al. (1975) reported a concentration of mixed xylenes of 0.29 mg/liter in the New Orleans drinking water; however, they did not specify the concentrations for individual isomers.

Ethylbenzene. Using gas chromatography, Burnham et al. (1976) found ethylbenzene in river water, chemical plant effluents, and

textile plant effluents, and well water in concentrations of approximately 15 ng/liter. In an EPA survey of contaminants in the drinking water of 10 U.S. cities, ethylbenzene was detected but not quantified in six samples (U.S. Environmental Protection Agency, 1975). The report of that survey indicated that the average concentration of alkylated benzenes in U.S. drinking water was 1 μ g/liter.

Styrene. Gas chromatography has been used to determine styrene in wastewaters in concentrations of 4.5-63 μ g/liter (Pakhomova and Berendeewa, 1974). Lower concentrations have been measured after extraction with freon and concentration of the sample in a Kuderna-Danish apparatus (Austern et al., 1975).

Styrene has also been detected in finished U.S. drinking water in concentrations of less than 1 μ g/liter (National Academy of Sciences, 1977; U.S. Environmental Protection Agency, 1975). For example, such concentrations have been found in commercial, charcoal-filtered drinking water in New Orleans, La. (Dowty et al., 1975).

Styrene concentrations of 1 μ g/liter have been detected in the Scheldt River in The Netherlands, in the Kanawha River in West Virginia (Eurocop-Cost, 1976), and in the effluent discharged from petroleum-refining (31 μ g/liter), chemical (30 μ g/liter), rubber (2.6-3 μ g/liter), and textile manufacturing plants (concentration not given) in the United States (Eurocop-Cost, 1976; Shackelford and Keith, 1976).

The extraction of benzene followed by polarography has been used in the Soviet Union to determine styrene in sewage from a plant producing plastic stabilizers (Meshkova and Dmitrieva, 1974) and in industrial effluent from polymer production. The concentrations ranged from 0.2 to 5.0 mg/liter (Dmitrieva et al., 1975).

BIOLOGICAL MONITORING

Toluene

The metabolism of toluene involves the formation of benzoic, hippuric, and methyl hippuric acids and conjugation prior to excretion. Capellini and Alessio (1971) measured the hippuric acid excreted in the urine of 19 control subjects and 17 workers who had been exposed for several years to toluene in mean atmospheric concentrations of 125 ppm. All samples were collected at the end of the working day. After solvent extraction with a mixture of isopropyl alcohol and diethylether, the samples were analyzed by the ultraviolet spectrophotometric method of Pagnotto and Lieberman (1967). The absorbance was measured at 230 nm.

Ellman et al. (1961) have reviewed the early methods of analyzing hippuric acid, which involved crystallization, ether extraction, determination of hippuric acid by weighing, titration, or Kjeldahl method. These methods are seldom used today because they are tedious and do not always provide accurate measurements of quantities. More acceptable procedures have been based on colorimetry (Gaffney et al., 1954; Ikeda and Ohtsuji, 1971; Ogata et al., 1969, 1970; Pagnotto and Lieberman, 1967; Umberger and Fiorese, 1963), fluorimetry (Ellman et al., 1961), and ultraviolet spectrophotometry (Elliott, 1957; Rieder, 1957). The specificity of some of the methods has been improved by first treating the sample with ion-exchange resin (Elliott, 1957), paper chromatography (Gaffney et al., 1954; Ikeda and Ohtsuji, 1971; Ogata et al., 1969), or alcohol-ether extraction (Pagnotto and Lieberman, 1967).

Although hippuric acid has been used to determine exposure to toluene, its accuracy may be compromised by the presence of dietary components that are metabolized to hippuric acid.

Xylenes

All three isomers of xylene are oxidized primarily to the corresponding o-, m-, or p-toluic acid (Bray et al., 1949). Most of the o-toluic acid is excreted unconjugated as an ester glucuronide. A small amount is excreted as a glycine conjugate. The m- and p-toluic acids are excreted chiefly as glycine conjugates. Only small amounts are excreted free or conjugated with glucuronic acid. There is some evidence that the benzene ring is hydroxylated to form phenolic metabolites (Bakke and Scheline, 1970; Bray et al., 1950). The inhalation experiments conducted by Ogata et al. (1970) indicated that 72% of absorbed m-xylene was excreted in the urine of male volunteers as m-methylhippuric acid during and within 18 hr after the end of exposure.

Ogata et al. (1969) have developed two analytical procedures for determining m- and p-methylhippuric acids in urine. Both are based on the formation of colored azlactone. In one method the methylhippuric acids are extracted with ethyl ether/ethyl alcohol solution and dried with silica gel. p-Dimethylaminobenzaldehyde in acetic anhydride is used to form azlactone. The azlactones are then extracted with ethyl ether, and the absorbance is read at 460 mμ. When standard solutions prepared by the same extraction procedure were applied to aqueous solutions of m- and p-dimethylaminobenzaldehyde reagent, a positive reaction with urea resulted. However, the extraction procedure using ethyl ether/ethyl alcohol did not extract urea from urine. The sensitivity of this method was 4 μg/ml urine.

The second method reported by Ogata et al. (1969) involves the use of benzenesulfonyl chloride. This method is less sensitive (20 µg/ml urine), but is much simpler to use. The methylhippuric acids are extracted with ethyl acetate or ethyl ether/ethyl alcohol solution. The azlactones are formed by reaction with benzenesulfonyl chloride in pyridine solution. The absorbance is then read at 380 nm against a pyridine-benzenesulfonyl chloride blank. The investigators reported from 94% to 100% recoveries by both methods.

Hippuric acid can also be determined by both methods. In addition, hippuric, m-methylhippuric, and p-methylhippuric acids can be separated by paper or thin-layer chromatography and then determined spectrophotometrically (Ogata et al., 1969).

Buchet and Lauwerys (1973) have described a gas chromatographic technique for the determination of both hippuric acid and m-methylhippuric acid in urine. This technique is as specific and sensitive as those reported by Ogata et al. (1969), but is much more rapid.

A known amount of heptadecanoic acid, as the internal standard, is added to urine before its extraction with ethyl acetate. After evaporation of the solvent, the acids are methylated with diazomethane. The residue is dissolved in methanol, which is then injected into the gas chromatograph. These investigators calculated the ratio of the height of the m-methylhippuric acid peak to the height of the heptadecanoic acid peak and determined the concentration of the acid in urine by reference to a calibration curve prepared under the same conditions (Buchet and Lauwerys, 1973).

Ethylbenzene

Ethylbenzene is absorbed chiefly via the inhalation route. A small proportion of the ethylbenzene that enters the bloodstream is exhaled unchanged, but most of it is excreted in urine as metabolites because of the oxidation of the side chain ($-\text{CH}_2-\text{CH}_3$) (Gerarde, 1963). The metabolism of ethylbenzene by humans has been studied by Bardodej and Bardodejova (1970). Using techniques such as paper chromatography (separation) and spectrophotometry (identification), the major metabolites found in the urine included mandelic acid (64%), phenylglyoxylic acid (25%), and 1-phenylethanol (5%). These authors were unable to identify several common metabolites of ethylbenzene, including acetophenone, phenylethyleneglycol, ω -hydroxyacetophenone, hippuric acid, and mercapturic acid, probably because their techniques lacked sensitivity (El Masry et al., 1956; Kiese and Lenk, 1974).

Conkle et al. (1975) reported that ethylbenzene is also present in cigarette smoke. These authors measured trace quantities of ethyl-

benzene in the expired air of eight male subjects ranging from 23 to 47 years of age. Their median age was 38. Using gas chromatographic techniques, they detected ethylbenzene in five of the eight subjects. The smokers in this group had the highest levels of ethylbenzene (0.78 to 14×10^{-6} g/hr).

Styrene

Epoxidation of the side-chain double bond ($-\text{CH}=\text{CH}_2$) causes styrene in the human body to be broken down by approximately 90% to form the two primary metabolites in the urine--mandelic acid and phenylglyoxylic acid (Bauer, 1979; Wolff *et al.*, 1978). Unlike most other procedures, the gas chromatographic determination of mandelic and phenylglyoxylic acids in urine is almost disturbance free. Therefore, it is an ideal method for biological monitoring of styrene-exposed workers. Mandelic acid can be measured easily with standard gas chromatographic methods (Engström and Rantanen, 1974; Engström *et al.*, 1976, 1978; Nicholson, 1969; Šedivec and Fajfrlik, 1970; Slob, 1973; Vivoli and Vecchi, 1974). In contrast, phenylglyoxylic acid is highly unstable--it can be made to form a derivative suitable for gas chromatographic analysis only with difficulty (Bauer, 1979; Bauer and Guillemin, 1976; Guillemin and Bauer, 1976).

To circumvent these analytical difficulties, Bauer and coworkers (Bauer, 1979; Guillemin and Bauer, 1978) have developed the following procedure for the total determination of both mandelic and phenylglyoxylic acids in the urine of workers exposed to styrene:

1. Urine samples are obtained at the beginning of the last working day of the week.
2. Immediately after the sample has been taken, the relatively unstable phenylglyoxylic acid is reduced with zinc and sulfuric acid to form the more stable mandelic acid.
3. The entire content of mandelic acid in the urine samples (mandelic acid plus phenylglyoxylic acid) is determined by gas chromatography following extraction and derivatization with trimethylsilylating reagent (TMS).

Sauerhoff *et al.* (1976) administered ^{14}C -labelled styrene to rats in doses of 500 mg/kg of body weight and 50 mg/kg of body weight. They reported that the labelled styrene was rapidly excreted in the urine with greater than 90% radioactivity. Urine samples were collected between 0 and 12 hr, 12 and 24 hr, and 24 and 36 hr after administration and were separated for metabolites by liquid chromatography with a glass column packed with Aminex 50H-4 hydrogen formate and an aqueous solution containing 10% acetonitrile and 2% acetic acid.

acid as eluent. The samples were methylated with diazomethane and then analyzed by parallel gas chromatography-mass spectrometry and gas proportional counter using OV-1 on a Chromosorb W column. When sample size permitted, both electron impact and chemical ionization mass spectra were determined. A total of seven ^{14}C -labelled urinary metabolites of styrene were isolated. Of these, only four were identified as mandelic, phenylglyoxylic, hippuric, and benzoic acids.

In another study on metabolism in rats using ^{14}C -labelled styrene, Pantarotto *et al.* (1978) observed the formation of phenolic metabolites such as 4-vinylphenol, *p*-hydroxymandelic acid, *p*-hydroxybenzoic acid, and *p*-hydroxyhippuric acid in addition to the expected metabolites such as phenylethyleneglycol, mandelic acid, benzoic acid, and hippuric acid. The urinary biotransformation products were characterized by mass spectrometry and by comparative thin layer chromatography with standard compounds.

Styrene Oxide

Leibman and Ortiz (1970) have used gas chromatography with flame ionization detection and thin-layer chromatography to identify metabolites of styrene oxide in biological media.

CONCLUSIONS

Several sampling and analytical methods can be used for the collection, identification, and quantification of toluene, *o*-, *m*-, and *p*-xylenes, ethylbenzene, cumene, styrene, and styrene oxide in air and water. The most specific and sensitive of these are gas chromatography-mass spectrometry with flame ionization (for toluene, *o*-, *m*-, *p*-xylenes, ethylbenzene, cumene, and styrene oxide) and electron capture detectors to detect styrene as its dibromide to measure parts per billion levels of these compounds in the ambient air, in water, and in the biological samples.

REFERENCES

- Altshuller, A. P., and T. A. Bellar. 1963. Gas chromatographic analysis of hydrocarbons in the Los Angeles atmosphere. *J. Air Pollut. Control Assoc.* 13:81-87.
- Altshuller, A. P., W. A. Lonneman, F. D. Sutterfield, and S. L. Kopczynski. 1971. Hydrocarbon composition of the atmosphere of the Los Angeles basin--1967. *Environ. Sci. Technol.* 5:1009-1016.
- Altwick, E. R., R. A. Whitby, and W. N. Stasiuk. 1977. Ambient hydrocarbon levels at two elevated and some street level sites. Pp. 520-523 in Kasuga, S., N. Suzuki, T. Yamada, G. Kimura, K. Inagaki, and K. Onoe, eds. *Proceedings of the 4th International Clean Air Congress, 1977. Japanese Union of Air Pollution Prevention Associations, Tokyo, Japan.* [Chem. Abs. 88:141039y, 1978.]
- American Conference of Governmental Industrial Hygienists. 1972. Pp. S-22, S-31, S-34, and S-46 in *Air Sampling Instruments for Evaluation of Atmospheric Contaminants*, 4th edition. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio.
- Andreatch, A. J., and R. Feinland. 1960. Continuous trace hydrocarbon analysis by flame ionization. *Anal. Chem.* 32:1021-1024.
- Anger, J., D. Szadkowski, A. Manz, R. Pett, and G. Lehnert. 1973. Chronische Lösungsmittelbelastung am Arbeitsplatz. I. Gaschromatographische Bestimmung von Benzol und Toluol in der Luft und im Dampfraum von Blutproben. (Occupational chronic exposure to organic solvents. I. Gas chromatographic determination of benzene and toluene in air and in the vapour phase of blood samples.) *Int. Arch. Arbeitsmed.* 31:1-8.
- Apol, A. G., W. A. Cook, and E. F. Lawrence. 1966. Plastic bags for calibration of air sampling devices--Determination of precision of method. *Am. Ind. Hyg. Assoc. J.* 27:149-153.
- Austern, B. M., R. A. Dobbs, and J. M. Cohen. 1975. Gas chromatographic determination of selected organic compounds added to wastewater. *Environ. Sci. Technol.* 9:588-590.
- Baernstein, H. D. 1943. Photometric determination of benzene, toluene, and their nitro derivatives. *Ind. Eng. Chem. Anal. Ed.* 15:251-253.

- Bakke, O. M., and R. R. Scheline. 1970. Hydroxylation of aromatic hydrocarbons in the rat. *Toxicol. Appl. Pharmacol.* 16:691-700.
- Balint, T., S. Igelewski, E. Kerenyi, J. Stumpfhauser, G. Kerenyi, and T. Molnar. 1974. Apparatus for measuring the concentrations of organic air contaminants. *Germ. Offen.* 2,424,436 (Cl.G Oln), 12 Dec. 1974; *Hung. Appl. MA-2477*, 23 May 1973. 15 pp. [Chem. Abs. 82:89709b, 1975.]
- Bardodej, Z., and E. Bardodejova. 1970. Biotransformation of ethyl benzene, styrene, and alpha-methylstyrene in man. *Am. Ind. Hyg. Assoc. J.* 31:206-209.
- Bauer, D. 1979. The application of toxicological criteria in the monitoring and evaluation of solvent exposure. Paper presented at the 6th International Colloquium on the Prevention of Industrial Accidents and Occupational Diseases in the Chemical Industry, Frankfurt, Federal Republic of Germany, June 18-20, 1979.
- Bauer, D., and M. Guillemin. 1976. Human exposure to styrene. I. The gas chromatographic determination of urinary phenylglyoxylic acid using diazomethane derivatization. *Int. Arch. Occup. Environ. Health* 37:47-55.
- Bertsch, W., E. Anderson, and G. Holzer. 1975. Trace analysis of organic volatiles in water by gas chromatography-mass spectrometry with glass capillary columns. *J. Chromatogr.* 112:701-718.
- Bos, R., R. Guicherit, and A. Hoogeven. 1977. Distribution of some hydrocarbons in ambient air near Delft and the influence on the formation of secondary air pollutants. *Sci. Total Environ.* 7:269-281.
- Bray, H. G., B. G. Humphris, and W. V. Thorpe. 1949. Metabolism of derivatives of toluene. 3. o-, m-, and p-Xylenes. *Biochem. J.* 45:241-244.
- Bray, H. G., B. G. Humphris, and W. V. Thorpe. 1950. Metabolism of derivatives of toluene. 5. The fate of the xylenols in the rabbit, with further observations on the metabolism of the xylenes. *Biochem. J.* 45:395-399.
- Bruderreck, H., W. Schneider, and I. Halász. 1964. Quantitative gas chromatographic analysis of hydrocarbons with capillary columns and flame ionization detector. *Anal. Chem.* 36:461-473.

- Buchet, J. P., and R. R. Lauwerys. 1973. Measurement of urinary hippuric and m-methylhippuric acids by gas chromatography. *Br. J. Ind. Med.* 30:125-128.
- Burchfield, H. P., and E. E. Storrs. 1962. Pp. 335-342 in *Bioclinical Applications of Gas Chromatography*. Academic Press, New York.
- Burnett, R. D. 1976. Evaluation of charcoal sampling tubes. *Am. Ind. Hyg. Assoc. J.* 37:37-45.
- Burnham, A. K., G. V. Calder, J. S. Fritz, G. A. Junk, H. J. Sveinsson, and R. Willis. 1972. Identification and estimation of new organic contaminants in potable water. *Anal. Chem.* 44:139-144.
- Campbell, E. E., and H. M. Ide. 1966. Air sampling and analysis with microcolumns of silical gel. *Am. Ind. Hyg. Assoc. J.* 27:323-331.
- Capellini, A., and L. Alessio. 1971. L'eliminazione urinaria dell'acido ippurico in operai esposti a toluolo. (The urinary excretion of hippuric acid in workers exposed to toluene.) *Lav. 62:196-201*.
- Coleman, W. E., R. D. Lingg, R. G. Melton, and F. C. Kopfler. 1971. The occurrence of volatile organics in five drinking water supplies using gas chromatography/mass spectrometry. Pp. 327-337 in L. H. Keith, ed. *Identification and Analysis of Organic Pollutants in Water*. Ann Arbor Science Publishers, Inc., Ann Arbor, Mich.
- Conkle, J. P., B. J. Camp, and B. E. Welch. 1975. Trace composition of human respiratory gas. *Arch. Environ. Health* 30:290-295.
- Cropper, F. R., and S. Kaminsky. 1963. Determination of toxic organic compounds in admixture in the atmosphere by gas chromatography. *Anal. Chem.* 35:735-743.
- Dambrauskas, T., and W. A. Cook. 1963. Methanol as the absorbent reagent in the determination of benzene, toluene, xylene and their mixtures in air. *Am. Ind. Hyg. Assoc. J.* 24:568-575.
- Davies, J. T. 1974. Migration of styrene monomer from packaging material into food. Experimental verification of a theoretical model. *J. Food Technol.* 9:275-283.

- Dmitrieva, V. N., O. V. Meshkova, and V. D. Bezuglyi. 1975. Determination of low contents of organic impurities in effluents from polymer production. *J. Anal. Chem. USSR* 30:1181-1183. [English translation.]
- Dolgoplov, V. D., and L. I. Lishcheta. 1971. Qualitative determination of by-products in commercial samples of styrene chlorohydrin. *Khim. Farm. Zh.* 5(11):55-56. [Chem. Abs. 76:27967b, 1972.]
- Dowty, B. J., D. R. Carlisle, and J. L. Laseter. 1975. New Orleans drinking water sources tested by gas chromatography-mass spectrometry: Occurrence and origin of aromatics and halogenated aliphatic hydrocarbons. *Environ. Sci. Technol.* 9:762-765.
- Elliott, H. C., Jr. 1957. Microdetermination of hippuric acid in urine. *Anal. Chem.* 29:1712-1715.
- Ellman, G. L., A. Burkhalter, and J. LaDou. 1961. A fluorometric method for the determination of hippuric acid. *J. Lab. Clin. Med.* 57:813-818.
- El Masry, A. M., J. N. Smith, and R. T. Williams. 1956. Studies in detoxication. 69. The metabolism of alkylbenzenes: n-Propylbenzene and n-butylbenzene with further observations on ethylbenzene. *Biochem. J.* 64:50-56.
- Engström, K., and J. Rantanen. 1974. A new gas chromatographic method for determination of mandelic acid in urine. *Int. Arch. Arbeitsmed.* 33:163-167.
- Engström, K., H. Harkonen, K. Pekari, and J. Rantanen. 1978. Evaluation of occupational styrene exposure by ambient air and urine analysis. *Scand. J. Work Environ. Health* 4(Suppl. 2):121-123.
- Engström, K., K. Husman, and J. Rantanen. 1976. Measurement of toluene and xylene by gas chromatography. *Int. Arch. Occup. Environ. Health* 36:153-160.
- Eurocop-Cost. 1976. P. 101 in *A Comprehensive List of Polluting Substances which have been Identified in Various Fresh Waters, Effluent Discharges, Aquatic Animals and Plants, and Bottom Sediments*. 2nd edition, EUCO/MDU/73/76, XII/476/76. Commission of the European Communities, Luxembourg.
- Feldstein, M., S. Balestrieri, and D. A. Levaggi. 1967. The use of silica gel in source testing. *Am. Ind. Hyg. Assoc. J.* 28:381-385.

- Gaffney, G. W., K. Schreier, N. DiFerrante, and K. I. Altman. 1954. The quantitative determination of hippuric acid. *J. Biol. Chem.* 206:695-698.
- Gage, J. C., N. Strafford, and R. Truhaut. 1962. Methods for the Determination of Toxic Substances in Air. Styrene, Method II, International Union of Pure and Applied Chemistry, Butterworths, London, England.
- Garrison, A. W. 1977. Part I. Occurrence and removal of water pollutants. Analysis of organic compounds in water to support health effects studies. Pp. 2-30 in H. F. Kraybill, C. J. Dawe, J. C. Harshbarger, and R. G. Tardiff, eds. Aquatic Pollutants and Biologic Effects with Emphasis on Neoplasms. Volume 28, Annals of the New York Academy of Sciences. New York Academy of Sciences, New York.
- Gerarde, H. W. 1963. The aromatic hydrocarbons. Pp. 1219-1232 in F. A. Patty, ed. Industrial Hygiene and Toxicology. 2, Toxicology. Interscience Publishers, New York.
- Graziani, G., S. Fati, and C. Pesaresi. 1970. Gas-chromatographic study of the coefficient of distribution of benzene in water. Relation to various ambient concentrations. *Folia Med. Biophys.* 53(2-3):51-61. [Chem. Abs. 75:96393c, 1971.]
- Guillemin, M., and D. Bauer. 1976. Human exposure to styrene. Quantitative and specific gas chromatographic analysis of mandelic and phenylglyoxylic acids as an index of styrene exposure. *Int. Arch. Occup. Environ. Health* 37:57-64.
- Guillemin, M. P., and D. Bauer. 1978. Biological monitoring of exposure to styrene by analysis of combined urinary mandelic and phenylglyoxylic acids. *Am. Ind. Hyg. Assoc. J.* 39:873-878.
- Halász, I., and W. Schneider. 1962. Quantitative gas chromatographic analysis of hydrocarbons with capillary column and flame ionization detector (II). Pp. 287-306 in N. Brenner, J. E. Callen, and M. D. Weiss, eds. Gas Chromatography. (Third International Symposium held under the Auspices of the Analysis Instrumentation Division of the Instrument Society of America, June 13-16, 1961.) Academic Press, New York.
- Hanson, N. W., D. A. Reilly, and H. E. Stagg, eds. 1965. Aromatic hydrocarbons (benzene, toluene, xylene). Pp. 51-55 in The Determination of Toxic Substances in Air. A Manual of ICI Practice. W. Heffer & Sons Ltd., Cambridge, Mass.

- Hay, E. B., III. 1964. Exposure to aromatic hydrocarbons in a coke oven by-product plant. *Am. Ind. Hyg. Assoc. J.* 25: 386-391.
- Holzer, G., H. Shanfield, A. Zlatkis, W. Bertsch, P. Juarez, H. Mayfield, and H. M. Liebich. 1977. Collection and analysis of trace organic emissions from natural sources. *J. Chromatogr.* 142:755-764.
- Hoshika, Y. 1977. Gas chromatographic determination of styrene as its dibromide. *J. Chromatogr.* 136:95-103.
- Hubbard, B. R., and L. Silverman. 1950. Rapid method for the determination of aromatic hydrocarbons in air. *AMA Arch. Ind. Hyg. Occup. Med.* 2:49-55.
- Ikeda, M., and H. Ohtsuji. 1971. Phenobarbital-induced protection against toxicity of toluene and benzene in the rat. *Toxicol. Appl. Pharmacol.* 20:30-43.
- Ioffe, B. V., V. A. Isidorov, and I. G. Zenkevich. 1977. Gas chromatographic-mass spectrometric determination of volatile organic compounds in an urban atmosphere. *J. Chromatogr.* 142:787-795.
- Kalliokoski, P., and P. Pfäffli. 1975. Charcoal sampling method for determining the concentration of styrene in air. *Scand. J. Work Environ. Health* 1:193-198.
- Keith, L. H., ed. 1976. Identification and Analysis of Organic Pollutants in Water. Ann Arbor Science Publishers, Inc., Ann Arbor, Mich. 718 pp.
- Keith, L. H., A. W. Garrison, F. R. Allen, M. H. Carter, T. L. Floyd, J. D. Pope, and A. D. Thruston, Jr. 1976. Identification of organic compounds in drinking water from thirteen U.S. cities. Pp. 329-373 in L. H. Keith, ed. Identification and Analysis of Organic Pollutants in Water. Ann Arbor Science Publishers, Inc., Ann Arbor, Mich.
- Khubulava, G. K., N. G. Sikharulidze, and R. V. Kobakhidze. 1973. Determination of small amounts of benzene in the air of industrial facilities. *Koks Khim.*, No. 5:36-37. [Chem. Abs. 79:34722h, 1973.]
- Kiese, M., and W. Lenk. 1974. Hydroxyacetophenones: Urinary metabolites of ethylbenzene and acetophenone in the rabbit. *Xenobiotica* 4:337-343.

- Kleopfer, R. D. 1976. Analysis of drinking water for organic compounds. Pp. 399-416 in L. H. Keith, ed. Identification and Analysis of Organic Pollutants in Water. Ann Arbor Science Publishers, Inc., Ann Arbor, Mich.
- Kleshcheva, M. S., V. T. Usacheva, and V. N. Pozharova. 1976. Determination of residual monomers and non-polymerizable impurities in polystyrene plastics by a gas-chromatographic method. Plast. Massy, Issue No. 7:57-58. [Chem. Abs. 130411u, 1971.]
- Kol'kovsky, P. 1967. A new color reaction for the vapor of some aromatic hydrocarbons. J. Anal. Chem. USSR 22:40 [English translation.]
- Kopfler, F. C., R. G. Melton, J. L. Mullaney, and R. G. Tarver. 1975. Human exposure to water pollutants. Natl. Meeting Environ. Chem., Am. Chem. Soc. 15(1):185-187.
- Kulicka, J., R. Baranowski, and Z. Gregorowicz. 1967. Thin layer chromatography of the oxidation products of ethylbenzene. Fresenius' Z. Anal. Chem. 230(5):357-359. [Chem. Abs. 104940f, 1967.]
- Kupel, R. E., and L. D. White. 1971. Report on a modified detection tube. Am. Ind. Hyg. Assoc. J. 32:456.
- Kusnetz, H. L., B. E. Saltzman, and M. E. Lanier. 1960. Calibration and evaluation of gas detecting tubes. Am. Ind. Hyg. Assoc. J. 21:361-373.
- Leibman, K. C., and E. Ortiz. 1970. Epoxide intermediates in the microsomal oxidation of olefins to glycols. J. Pharmacol. Exp. Ther. 173:242-246.
- Leonard, M. J., E. L. Fisher, M. F. Brunelle, and J. E. Dickerson. 1976. Effects of the motor vehicle control program on hydrocarbon concentrations in the central Los Angeles basin. J. Air Pollut. Control Assoc. 26:359-363.
- Lonneman, W. A., T. A. Bellar, and A. P. Altshuller. 1968. Aromatic hydrocarbons in the atmosphere of the Los Angeles basin. Environ. Sci. Technol. 2:1017-1020.
- Maffett, P. A., T. F. Doherty, and J. L. Monkman. 1956. A simple method for the collection and determination of micro amounts of benzene or toluene in air. Am. Ind. Hyg. Assoc. Q. 17:188.

- Markelov, M. A., and E. I. Semenenko. 1976. Determination of microconcentrations of substances migrating from polymer materials to water. *Plast. Massy*, No. 1:57-59. [Chem. Abs. 84:155747g, 1976.]
- McKinney, J. D., R. R. Maurer, J. R. Hass, and R. O. Thomas. 1976. Possible factors in the drinking water of laboratory animals causing reproductive failure. Pp. 417-432 in L. H. Keith, ed. *Identification and Analysis of Organic Pollutants in Water*. Ann Arbor Science Publishers, Inc., Ann Arbor, Mich.
- Meshkova, O. V., and V. N. Dmitrieva. 1974. Extraction-polarographic determination of styrene and methyl methacrylate in industrial waste waters. *Zavod. Lab.* 40(1):28-29. [Chem. Abs. 81:16386p, 1974.]
- Mishmash, H. E., and C. E. Meloan. 1972. Indirect spectrophotometric determination of nanomole quantities of oxiranes. *Anal. Chem.* 44:835-836.
- Murav'eva, S. I., and N.Ya. Smolyar. 1974. Determination of styrene in the biological fluids of experimental animals. *Gig. Tr. Prof. Zabol.*, No. 9:52-53. [Chem. Abs. 82:167113u, 1975.]
- National Academy of Sciences. 1977. Styrene. Pp. 763-765 in *Safe Drinking Water and Health*. A report prepared by the Safe Drinking Water Committee. National Academy of Sciences, Washington, D.C.
- National Institute for Occupational Safety and Health. 1977a. Cumene. Pp. S23-1 to S23-8 in *NIOSH Manual of Analytical Methods*, 2nd edition. Part II. Standards Completion Program Validated Methods, Volume 2. D. G. Taylor, Manual Coordinator. NIOSH Publication No. 77-157-B. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio.
- National Institute for Occupational Safety and Health. 1977b. Ethylbenzene. Pp. S29-1 to S29-8 in *NIOSH Manual of Analytical Methods*, 2nd edition. Part II. Standards Completion Program Validated Methods, Volume 2. D. G. Taylor, Manual Coordinator. NIOSH Publication No. 77-157-B. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio.

- National Institute for Occupational Safety and Health. 1977c. Styrene. Pp. S30-1 to S30-8 in NIOSH Manual of Analytical Methods, 2nd edition. Part II. Standards Completion Project. Validated Methods, Volume 2. D. G. Taylor, Manual Coordinator. NIOSH Publication No. 77-157-B. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio.
- National Institute for Occupational Safety and Health. 1977d. Toluene. Pp. S343-1 to S343-8 in NIOSH Manual of Analytical Methods, 2nd edition. Part II. Standards Completion Project. Validated Methods, Volume 3. D. G. Taylor, Manual Coordinator. NIOSH Publication No. 77-157-C. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio.
- National Institute for Occupational Safety and Health. 1977e. Xylene. Pp. S318 to S318-8 in NIOSH Manual of Analytical Methods, 2nd edition. Part II. Standards Completion Project. Validated Methods, Volume 3. D. G. Taylor, Manual Coordinator. NIOSH Publication No. 77-157-C. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio.
- Neligan, R. E., M. J. Leonard, and R. J. Bryan. 1965. The gas chromatographic determination of aromatic hydrocarbons in atmosphere. Natl. Meet., Div. Water, Air, Waste Chem., Am. Chem. Soc. 5(2):118-121.
- Nicholson, J. D. 1969. The determination of mandelic acid in urine. Analyst 94:413-416.
- Ogata, M., K. Tomokuni, and Y. Takatsuka. 1969. Quantitative determination in urine of hippuric acid and m- or p-methylhippuric acid, metabolites of toluene and m- or p-xylene. Br. J. Ind. Med. 26:330-334.
- Ogata, M., K. Tomokuni, and Y. Takatsuka. 1970. Urinary excretion of hippuric acid and m- or p-methylhippuric acid in the urine of persons exposed to vapours of toluene and m- or p-xylene as a test of exposure. Br. J. Ind. Med. 27:43-50.
- Olishifski, J. B., and F. E. McElroy, eds. 1971. Pp. 68-76 in Fundamentals of Industrial Hygiene. National Safety Council, Chicago, Ill.

- Otterson, L. S., and C. S. Guy. 1964. A method of atmospheric solvent vapor sampling on activated charcoal in connection with gas chromatography. Pp. 37-43 in *Translations of the Twenty-Sixth Annual Meeting of the American Conference of Governmental and Industrial Hygienists*, Philadelphia, Penna., April 25-28, 1964. American Conference of Governmental and Industrial Hygienists, Cincinnati, Ohio.
- Pagnotto, L. D., and L. M. Lieberman. 1967. Urinary hippuric acid excretion as an index of toluene exposure. *Am. Ind. Hyg. Assoc. J.* 28:129-134.
- Pakhomova, A. D., and V. L. Berendeeva. 1974. Identification of styrene in waste waters. *Khim. Tekhnol. (Kiev)* Issue No. 3: 12-13. [Chem. Abs. 81:158428c, 1974.]
- Pantarotto, C., R. Fanelli, F. Bidoli, P. Morazzoni, M. Salmona, and K. Szczawinska. 1978. Arene oxides in styrene metabolism, a new perspective in styrene toxicity? *Scand. J. Work Environ. Health* 4(Suppl. 2):67-77.
- Parkes, D. G., C. R. Ganz, A. Polinsky, and J. Schulze. 1976. A simple gas chromatographic method for the analysis of trace organics in ambient air. *Am. Ind. Hyg. Assoc. J.* 37:165-173.
- Pellizzari, E. D. 1979. Information on the Characterization of Ambient Organic Vapors in Areas of High Chemical Pollution. Control No. 68-02-2721, Health Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, N.C. 134 pp.
- Pellizzari, E. D., J. E. Bunch, R. E. Berkley, and J. McRae. 1976. Determination of trace hazardous organic vapor pollutants in ambient atmospheres by gas chromatography/mass spectrometry/computer. *Anal. Chem.* 48:803-807.
- Petrova, L. I., Z. K. Boikova, and Z. G. Guricheva. 1974. Spectrophotometric determination of small amounts of styrene in extracts in the presence of low-molecular-weight substances. *Plast. Massy*, Issue No. 3:72-74. [Chem. Abs. 81:121536k, 1974.]
- Pilar, S., and W. F. Graydon. 1973. Benzene and toluene distribution in Toronto atmosphere. *Environ. Sci. Technol.* 7:628-631.
- Rappaport, S. M. 1975. The identification of effluents from rubber vulcanization. Pp. 185-216 in F. A. Ayer, ed. *Environmental Aspects of Chemical Use in Rubber Processing Operations*, Conference Proceedings (March 1975, Akron, Ohio). Report No. EPA-560/1-75-002. (Available from National Technical Information Service, Springfield, Va., as PB-244 172.) U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, D.C.

- Rappaport, S. M., and D. A. Fraser. 1976. Gas chromatographic-mass spectrometric identification of volatiles released from a rubber stock during simulated vulcanization. *Anal. Chem.* 48:476-481.
- Reid, F. H., and W. R. Halpin. 1968. Determination of halogenated and aromatic hydrocarbons in air by charcoal tube and gas chromatography. *Am. Ind. Hyg. Assoc. J.* 29:390-396.
- Rieder, H. P. 1957. Bestimmung von Benzoesäure neben Hippursäure mit Hilfe einer differential-spektrophotometrischen Methode. *Clin. Chim. Acta* 2:497-501.
- Roy, S. S. 1977. Titrimetric determination of residual monomer in styrene-acrylonitrile copolymers. *Analyst* 102:302-305.
- Russell, P. A. 1977. Denver Air Pollution Study--1973. *Proc. of a Symposium. Volume II, Final Report, January 1974-June 1974*. Report No. EPA/600/9-77/001. (Available from National Technical Information Service, Springfield, Va., as PB-264 216/3BE. Denver Research Institute, Colorado Environmental Science Research Laboratory, Research Triangle Park, N.C.)
- Sauer, T. C., Jr., W. M. Sackett, and L. M. Jeffrey. 1978. Volatile liquid hydrocarbons in the surface coastal waters of the Gulf of Mexico. *Mar. Chem.* 7:1-16.
- Sauerhoff, M. W., E. O. Madrid, and W. H. Bairn. 1976. The Fate of Orally Administered Styrene in Rats. *Toxicology Research, Health and Environmental Research*, Dow Chemical USA, Midland, Mich. [44] pp.
- Saunders, R. A., C. H. Blachly, T. A. Kovacina, R. A. Lamontagne, J. W. Swinnerton, and F. E. Saalfeld. 1975. Identification of volatile organic contaminants in Washington, D.C. municipal water. *Water Res.* 9:1143-1145.
- Scheiman, M. A., R. A. Saunders, and T. E. Saalfeld. 1974. Organic contaminants in the District of Columbia water supply. *Bull. Mass Spectrom.* 1:209-211.
- Sedivec, V., and J. Flek. 1970. Bestimmung toxischer Substanzen und ihrer Metaboliten in biologischen Flüssigkeiten mittels der Gaschromatographie. IV. Mandelsäure im Urin. *Collection Czech. Chem. Commun.* 35:931-937.
- Shackelford, W. M., and L. H. Keith. 1976. Pp. 213-214 in *Final Report of Organic Compounds Identified in Water*. Report No. EPA-600/4-76-062. U.S. Environmental Protection Agency, Office of Research and Development, Environmental Research Laboratory, Athens, Ga.

- Siegel, D., F. Müller, and K. Neuschwander. 1974. Vollautomatische Messung von Kohlenwasserstoff-Immissionen. Selektive Messung von C₁-C₅-KWW, C₆-KWW, Benzol. (Fully automotive measurement of hydrocarbon emission. Selective measurement of C₁-C₅ hydrocarbons and benzene.) Chromatographia 7:399-406.
- Singh, H. B., L. J. Salas, A. Smith, and H. Shigeishi. 1979. Atmospheric Measurements of Selected Toxic Organic Chemicals. Interim Report prepared for the U.S. Environmental Protection Agency, Research Triangle Park, N.C. by Stanford Research Institute International, Menlo Park, Calif.
- Slob, A. 1973. A new method for determination of mandelic acid excretion at low-level styrene exposure. Br. J. Ind. Med. 30:390-393.
- Smith, B. S., and J. O. Pierce. 1970. The use of plastic gas for industrial air samplings. Am. Ind. Hyg. Assoc. J. 31:343-348.
- Steichen, R. J. 1976. Modified solution approach for the gas chromatographic determination of residual monomers by headspace analysis. Anal. Chem. 48:1398-1402.
- Stephens, E. R. 1973. Hydrocarbons in Polluted Air: Summary Report. Coordinating Research Council Report CRC-APRAC-CAPA-5-68-1. (Available from National Technical Information Service, Springfield, Va., as PB-230 993.) Statewide Air Pollution Research Center, University of California, Riverside, Calif. 86 pp.
- Suffet, I. H., and J. V. Radziul. 1976. Analysis of organic pollutants in drinking water. International Conference on Environmental Sensing and Assessment, September 14-19, Las Vegas, Nevada, Volume 2, Paper 30-1. Institute of Electrical and Electronics Engineers, Inc., New York.
- Suta, B. E. 1979. Nonoccupational Exposures to Alkylbenzenes from Their Use as Solvents. Stanford Research Institute International, Menlo Park, Calif. [57] pp.
- Švob, V., and D. Deur-Šiftar. 1974. Kováts retention indices in the identification of alkylbenzene degradation products. J. Chromatogr. 91:677-689.
- Swan, J. D. 1954. Determination of epoxides with sodium sulfite. Anal. Chem. 26:878-880.
- Swiatecka, M., and H. Zowall. 1975. Determination of residual blowing agent and styrene in styrofoam by gas chromatography. Polimery (Warsaw) 20:33-34. [Chem. Abs. 84:5742n, 1976.]

- Umberger, C. J., and F. F. Fiorese. 1965. Colorimetric method for hippuric acid. Clin. Chem. 9:91-96.
- U.S. Environmental Protection Agency. 1975. Preliminary Assessment of Suspected Carcinogens in Drinking Water: Report to Congress Report No. EPA-560/4-75-005. (Available from National Technical Information Service, Springfield, Va., as PB-250 961.) U.S. Environmental Protection Agency, Office of Toxic Substances Washington, D.C. 107 pp.
- van Bogaert, M., B. Rollmann, G. Noël, M. Roberfroid, and M. Merx. 1978. A very sensitive gas chromatographic method for the detection of styrene oxidase and styrene oxide hydratase activities. Arch. Toxicol. (Suppl. 1):295-298.
- VanderKolk, A. L., and D. E. VanFarowe. 1965. Use of mylar bag for air sampling. Am. Ind. Hyg. Assoc. J. 26:321-322.
- Vivoli, G., and G. Vecchi. 1974. Ricerche sulle escrezioni urinarie di acido mandelico quale test di esposizione allo stirolo. Umano 26:1-9.
- Wancheck, P. L., and L. E. Wolfram. 1976. Qualitative analysis of styrene monomer in styrene/butadiene latexes using Raman spectroscopy. Appl. Spectrosc. 30:542-544.
- Ward, D. J. 1965. Cumene. Pp. 543-546 in H. F. Mark, J. J. Meehan Jr., and D. F. Othmer, eds. Kirk-Othmer Encyclopedia of Chemical Technology, 2nd edition, Volume 6. Interscience, New York.
- White, L. D., D. G. Taylor, P. A. Mauer, and R. E. Kupel. 1970. A convenient optimized method for the analysis of selected solvent vapors in the industrial atmosphere. Am. Ind. Hyg. Assoc. J. 31:225-232.
- Whitman, N. E., and A. E. Johnston. 1964. Sampling and analysis of aromatic hydrocarbon vapors in air: A gas-liquid chromatographic method. Am. Ind. Hyg. Assoc. J. 25:464-469.
- Williams, I. H. 1965. Gas chromatographic techniques for the identification of low concentrations of atmospheric pollutants. Anal. Chem. 37:1723-1732.
- Wolff, M. S., S. M. Daum, W. V. Lorimer, and I. J. Selikoff. 1978. Styrene and related hydrocarbons in subcutaneous fat from polyimination workers. J. Toxicol. Environ. Health 2:997-1004.
- Wolff, M. S., R. Lilis, W. V. Lorimer, and I. J. Selikoff. 1978. Biological indicators of exposure in styrene polymerization workers. Styrene in blood and adipose tissue and mandelic and phenylglyoxylic acids in urine. Scand. J. Work Environ. Health 4(Suppl. 2):114-118.

- Wronski, S., R. Pohorecki, and H. Wadolowski. 1972. Adsorption of benzene vapors from water vapor-containing air on active carbon. Pr. Inst. Inz. Chem. Politech. Warsz. 1:43-55. [Chem. Abs. 79:10169g, 1973.]
- Yamashita, T., H. Katsura, and Y. Mori. 1976. Hygienic study on polystyrene containers. I. Determination of trace amounts of styrene monomer in milk products. Shokuhin Eiseigaku Zasshi 17:187-192. [Chem. Abs. 85:61572q, 1976.]
- Yant, W. P., S. J. Pearce, and H. H. Schrenk. 1936. A microcolorimetric method for the determination of toluene. U.S. Department of the Interior, Bureau of Mines. Report of Investigations No. 3323. 12 pp. [Chem. Abs. 32:17287, 1937.]
- Zizin, V. G., M. G. Kazakova, I. F. Fainulin, and Yu.V. Perina. 1974. Determination of monomers in polymer products. Zavod. Lab. 40:929-931. [Chem. Abs. 82:18285z, 1975.]

CHAPTER 4

ENVIRONMENTAL DISPOSITION

The alkyl derivatives of benzene are major industrial chemicals, and several of them rank high among chemicals manufactured in the greatest volumes. Furthermore, they comprise a significant fraction of crude petroleum. This content is routinely increased during refining to various types of fuels and solvents. As discussed in Chapter 1, fuel and solvent usage probably account for the bulk of the emission of these compounds. Thus, we would expect and indeed do find that alkyl benzenes are prominent environmental pollutants. They are emitted primarily into the atmosphere, but they are also discharged into water or onto land. Alkyl benzenes can affect the environment directly, in compound-specific physical or biological processes, or indirectly, through the action of their intermediate degradation products. They also promote the formation of ozone and other symptoms of photochemical air pollution.

This chapter is concerned with the concentrations of alkyl benzenes in the atmosphere and in the aquatic environment as well as with the chemical and physical transformation processes undergone by these compounds under environmental conditions. Also included are considerations of the transport and longevity of alkyl benzenes in the environment.

It is likely that the chief environmental effect of alkyl benzenes is their promotion of photochemical air pollution. They share this effect with other classes of hydrocarbons and, consequently, are already subject to emission control. The main symptoms of their reactions in the atmosphere are the formation of the oxidants ozone and peroxy nitrates. They may contribute to the formation of atmospheric photochemical aerosols as well.

ATMOSPHERIC CONCENTRATIONS

Alkyl benzenes are prominent constituents of urban air, typically comprising between 25% and 40% of the total concentration of non-methane hydrocarbons (Hendry, 1979). In addition to pure and distilled solvents, major sources of these hydrocarbons are undoubtedly gasoline and its combustion in automobiles and, to a lesser extent, diesel fuel (as discussed in Chapter 1).

Estimates of total rates of release of environmental contaminants are useful in determining sources, but for assessing potential impact they are not as useful as measurements of actual ambient concentrations

Although there is no routine monitoring network for ambient concentrations of alkyl benzenes, reliable assessments can be made from urban levels. Using gas chromatography, especially capillary gas chromatography, it is possible to separate, identify, and quantify a large fraction of the hundred-plus species of hydrocarbons in urban air.

The concentrations of individual compounds determined in studies are listed in Table 4-1. From these data it is apparent that toluene is the most prevalent aromatic, followed by the xylenes and benzene. In many cases, the urban atmospheric distribution of alkyl benzene compounds is similar to their concentration in gasoline. In fact, Pilar and Graydon (1973), who measured the ratio of aromatic toluene to benzene in Toronto, Canada, concluded that the major source of both compounds was evaporation of gasoline or emissions resulting from the combustion of gasoline. Conversely, Lonnema et al. (1968) reported higher ratios of toluene to benzene in the atmosphere than in auto exhaust. They suggested that there may be important sources of toluene in addition to gasoline. A prime candidate for such an additional source would be solvents. Diurnal patterns of alkyl benzenes in the past have shown a strong peak correlating with the typical low atmospheric inversion during morning rush-hour traffic in Los Angeles (Figure 4-1). However, more recent data are desirable since automobile emission controls may have changed these patterns.

Leonard et al. (1976) evaluated the changing pattern of hydrocarbons in the Los Angeles atmosphere. During 1963-1965, before exhaust controls were required for new motor vehicles, the concentration of toluene was 59 ppb. In 1971 and 1973, after exhaust controls were implemented, the concentrations were 50 and 22 ppb, respectively. Singh et al. (1978) reported that the average levels of toluene in Los Angeles air were 11.7 ppb. As pointed out by Suta (1979), there was a clear-cut decline between 1963 and 1978. This probably resulted directly from the implementation of automotive air pollution controls. However, this is not necessarily true for all areas of the country since total nonmethane hydrocarbons in Texas have not been found to show a decline (Tannahill, 1976). This may reflect differences in hydrocarbon sources, which are dominated by the petroleum industry in this part of the country. Since most areas in the United States are heavily influenced by hydrocarbon emissions from motor vehicles, a decline due to controls seems likely.

There is a considerable amount of data pertaining to atmospheric concentrations of toluene (Table 4-2). Recently, Pellizzari (1978) has measured a large number of hydrocarbons, including alkyl benzenes, near manufacturing or refining sites in the United States. Average values of his data are presented in Table 4-3. It is possible that much of the alkyl benzenes measured in Pellizzari's study originated

Concentration, ppb by volume					
Los Angeles, California			Azusa, California		
Compound	Early morning		Downtown		
	Average, 1968 ^a	Average, 1966 ^b	Highest, 1966 ^b	Average, 1967 ^c	
1,2-Dichlorobenzene	NR ^d	15	57	NR	NR
1,3-Dichlorobenzene	39	37	129	30	14
1,4-Dichlorobenzene	12	6	25	5	2
1,2,3-Trichlorobenzene	13	16	61	12	5.5
1,2,4-Trichlorobenzene	11	8	33	6.5	3
1,3,5-Trichlorobenzene	8	6	22	5	2.5
1,4-Dichlorobenzene	12	2	6	NR	NR
1,2-Dichlorobenzene	12	NR	27	NR	NR
1,3-Dichlorobenzene	12	8	NR	NR	NR
1,4-Dichlorobenzene	2	2	6	NR	NR
1,2-Dichlorobenzene	2	NR	NR	NR	NR
1,3-Dichlorobenzene	NR	NR	NR	NR	NR
1,4-Dichlorobenzene	14	9	30	NR	NR
1,2,3-Trichlorobenzene	15	NR	NR	NR	NR
1,3,5-Trichlorobenzene	3	3	11	NR	NR
1,2,4-Trichlorobenzene	8	3	12	NR	NR
1,3,5-Trichlorobenzene	10	NR	NR	NR	NR
TOTAL SAMPLES ANALYZED	200	106	330	NR	NR

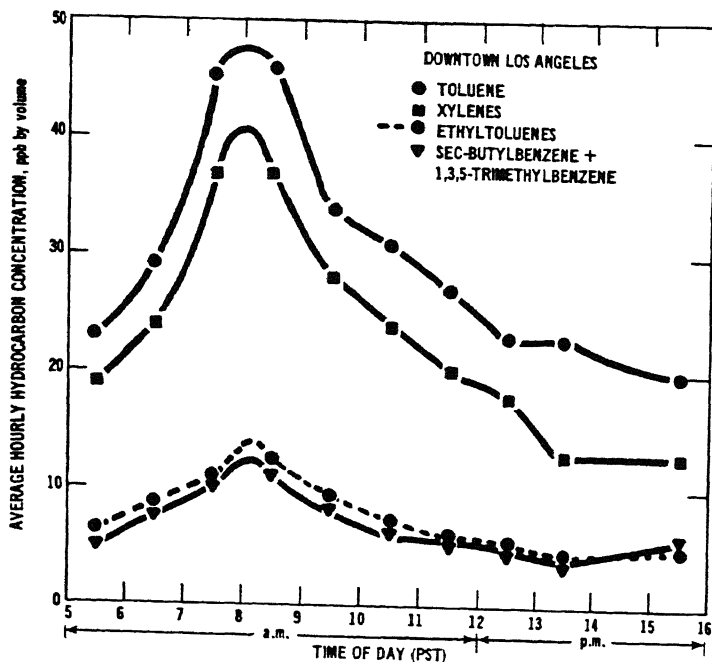


FIGURE 4-1. Diurnal variations in average hourly concentration of toluene, xylene, ethyltoluene, sec-butylbenzene and 1,3,5-trimethylbenzene in downtown Los Angeles. Data from Lonneman *et al.*, 1968. Figure from National Academy of Sciences, 1976.

TABLE 4-2. Atmospheric Concentrations of Toluene

Location	Year	Concentration, ppb	
		Average	Highest, or
Los Angeles, Calif.	1963-1965 ^a	59	NR ^b
	1966 ^c	37	129
	1967 ^d	30	50 ^d
	1968 ^e	39 ^e	NR
	1971 ^a	50	NR
	1973 ^a	22	NR
	1979 ^f	11.7	1.1-53.4
Azusa, Calif.	1967 ^d	14	23 ^d
Riverside, Calif.	1970-1971 ^g	--	9-18
Brethway-Gunderson Hill, Wash. ^h	1971 ⁱ	0.1	--
Camel's Hump, Vt. ^h	1971 ⁱ	1.0	--
Hells Canyon, Idaho ^h	1971 ⁱ	0.3	--
Moscow Mt., Idaho ^h	1971 ⁱ	0.2	--
Point Reyes, Calif.	1971 ⁱ	0.2	--
Toronto, Canada	1971 ^j	30	
Denver, Colo.	1973 ^k	9	74
Phoenix, Ariz.	1979 ^f	8.6	0.54-38.7
Oakland, Calif.	1979 ^f	3.1	0.15-16.9
Albany, N.Y.	NR ^{b,l}	1.3	NR ^b
Baton Rouge, La.	NR ^{b,m}	0.14	0.03-.23
Birmingham, Ala.	NR ^{b,m}	2.0	0.21-4.7
El Dorado, Ark.	NR ^{b,m}	11.0	2.5-13.6
Elizabeth, N.J.	NR ^{b,m}	17.0	1.9-39.1
El Paso, Tex.	NR ^{b,m}	4.9	0.05-18.8

TABLE 4-2. Atmospheric Concentrations of Toluene (cont'd)

Location	Year	Concentration, ppb	
		Average	Highest
Grand Canyon, Ariz.	NR ^{b,m}	Trace	
Houston, Tex.	NR ^{b,m}	1.6	0.21
Magma, Utah	NR	0.35	0.2
So. Charleston, W. Va.	NR ^{b,m}	0.05	0.0
Troy, N.Y.	NR ^{b,l}	1.0	
Upland, Calif.	NR ^{b,m}	7.3	0.78

^aLeonard et al., 1976.

^bNot reported.

^cLonneman et al., 1968.

^dAltshuller et al., 1971. Highest concentration is that exceeded by 10% of the measured values.

^eKopczynski et al. 1972. A single measurement was made.

^fSingh et al., 1979.

^gStephens, 1973.

^hSelected as remote air samples based on remote sampling location or origin of air in remote locations.

ⁱRobinson et al., 1973.

^jPilar and Graydon, 1973.

^kRussell, 1977.

^lAltwick et al., 1977.

^mPellizzari, 1979.

4-3. Average Concentrations of Benzene and Its Alkyl Derivatives in Air Near Chemical Manufacturing Sites in the United States^a

	Average Concentrations, ppb (number of samples)						
	Baton Rouge, La. (N=4)			Magma-Salt Lake City, Utah ^b (N=5)			
und	Birmingham, Ala. (N=5)	Houston, Tex. (N=5)	Upland, Calif. (N=5)	El Paso, Tex. (N=37)	El Dorado, Ark. (N=10)	Elizabeth, N.J. (N=10)	
ne	0.86	0.19	6.7	0.08	5.7	2.1	80
ne	2.0	0.14	1.6	0.35	7.3	4.9	11
benzene	NR ^c	0.009	0.12	0.047	0.50	4.7	2.6
ene	0.17	0.018	0.064	0.066	0.85	4.7	2.2
ene	0.80	0.033	0.16	0.19	2.8	1.4	6.1
yltoluene	0.12	0.017	0.040	0.054	0.25	0.31	1.6
ne	0.029	0.002	0.029	0.016	0.064	4.8	0.24
-Trimethyl- zene	0.054	0.005	0.008	0.017	0.13	0.089	19.0
							0.58

age values computed from data of Pellizzari, 1979.

cted as a background site.

from the use of solvents and automobiles. However, the ratios of toluene to benzene indicate that manufacturing was probably a factor in ambient concentrations at many of the sites.

The effect of industrial solvent use on atmospheric concentrations of alkyl benzenes has been studied by Sexton and Westberg (1980). They measured atmospheric hydrocarbon levels downwind from one of the largest U.S. automobile manufacturing plants (Table 4-4). Most of the hydrocarbons in the plume were alkyl benzenes (82% by weight). Toluene alone comprised more than half of the concentration of non-methane hydrocarbons. The concentration of toluene was still more than 15 ppb, 18 km downwind of the plant. This concentration may be compared to average toluene measurements summarized in Table 4-2 in many locations in the United States, and is comparable to or higher than most of these values.

Robinson et al. (1973) have measured the concentration of toluene in remote locations away from urban and industrial influences and found levels that ranged from 0.005 to 0.18 ppb in tropical and polar maritime air in 1971. Much higher levels (1 and 15 ppb) were measured in equatorial regions over land. Since anthropogenic sources are extremely unlikely in those regions, it is possible that such levels are associated with volatile emissions from plants. However, these high levels are surprising, and confirmation would be desirable.

In summary, concentrations of alkyl benzenes have declined significantly [by a factor of 5, as shown by the studies of Leonard et al. (1976) and Singh et al. (1979)] in the last 15 years in Los Angeles, presumably as a result of automotive emission controls. Concentrations of toluene (the most abundant alkyl benzene) in many urban areas of the United States in recent years ranged from less than 0.1 ppb to as much as 50 ppb, averaging approximately 1 to 10 ppb. In remote locations of the United States, they averaged approximately 0.2 ppb in 1971, but current levels may be lower, in line with decreased urban measurements. Recent measurements of only trace levels at the Grand Canyon (Table 4-2) seem to support this contention. Concentrations of the individual C_8 alkyl benzenes will be somewhat lower than those of toluene if gasoline is the major source (e.g., Table 4-1), but may be as much as an order of magnitude lower if manufacturing or solvent use is the source (Tables 4-3 and 4-4). The higher members of the homologous series continue this decrease in concentration.

ATMOSPHERIC CHEMISTRY OF ALKYL BENZENES

Alkyl benzenes can reside in the atmosphere for hours or days. Thus, they are prime candidates for short- and long-range transport away from urban emission sources. In the course of this transport

TABLE 4-4. Concentrations of Alkyl Benzenes Downwind from a Large Auto Manufacturing Plant^a

Compound	Concentration, ppb, by Distance Downwind, km				
	6	10.5	13.5	16.5	Background
Toluene	20.5	22.9	17.5	15.1	1.5
Ethylbenzene	2.7	1.5	1.2	1.2	0.35
<u>m</u> - and <u>p</u> -Xylene	5.2	4.4	3.4	3.2	0.59
<u>o</u> -Xylene	1.6	1.4	1.1	1.1	0.1
<u>n</u> -Propylbenzene	0.21	0.21	0.21	0.21	--
<u>p</u> -Ethyltoluene	0.52	0.42	0.42	0.42	0.10
<u>m</u> -Ethyltoluene	0.31	0.31	0.31	0.31	--
<u>o</u> -Ethyltoluene	0.42	0.31	0.21	0.42	0.10
1,3,5-Trimethylbenzene	0.31	0.31	0.21	0.31	--
1,2,4-Trimethylbenzene	0.73	0.73	0.52	0.72	0.21
1,3-Diethylbenzene	NR ^b	NR	0.10	NR	NR

^aReprinted with permission from Environmental Science and Technology Copyright 1980 American Chemical Society. From Sexton and Westberg, 1980.

^bNot reported.

they, like other hydrocarbons, undergo chemical transformation, thereby contributing to the increasingly pervasive phenomenon of photochemical air pollution.

Atmospheric alkyl benzenes are very stable in the dark when free radical initiators are absent. The solar spectrum in the troposphere does not contain much light in wavelengths shorter than 295 nm. Therefore, although the alkyl benzenes absorb strongly deeper into the ultraviolet range, they absorb only insignificant amounts of sunlight in the lower atmosphere. An exception is styrene (Calvert and Pitts, 1966). Despite the above limitations of the physical and chemical removal processes for alkyl benzenes, these compounds do in fact participate actively in the chemistry of urban and suburban atmospheres. Their reactions, like those of the alkenes, are initiated or catalyzed by photochemically produced radicals.

Chemical Removal Processes

Alkyl benzenes are apparently removed from the atmosphere essentially through free radical chain processes. Of the free radicals in the atmosphere, hydroxyl ($\cdot\text{OH}$), atomic oxygen (O), and peroxy radicals ($\text{HO}_2\cdot$ or $\text{RO}_2\cdot$, where R is an alkyl or acyl group) are potential candidates for the removal of alkyl benzenes. An additional reactive species is ozone (O_3). Reactions of singlet oxygen ($^1\text{O}_2$), although the subject of considerable study and speculation, are probably of no importance (Demerjian *et al.*, 1974). The concentration of ozone is routinely measured in the atmosphere, and the concentration of atomic oxygen may be easily estimated from ambient concentrations of nitrogen dioxide (NO_2) and ozone and from the solar intensity, since photolysis of these two molecules provides the only known source. Concentrations of hydroperoxy radicals have not been measured in polluted atmospheres, but they may be estimated from computer simulation of the relevant chemical processes.

Concentrations of hydroxyl radical have been measured several times in polluted and especially clean atmospheres, and its ambient concentration in Los Angeles has been estimated from hydrocarbon decay rates on one day. An estimate based on the rate at which ambient nitrogen dioxide is removed in Los Angeles has been made reasonably well. Additional values are derived from estimates of halocarbon lifetimes and from global photochemical models. The measurements and estimates for hydroxyl radicals and other reactive intermediates are summarized in Table 4-5.

Table 4-6 summarizes the rate constants for the reaction of these species with toluene, the most prevalent of the atmospheric alkyl benzenes. From data such as these, Hendry (1979) has calculated the chemical lifetime of toluene reacting with the various species and concluded that reaction with the hydroxyl radical is its only important reaction. Thus, concentrations of hydroxyl r

TABLE 4-5. Measurements or Estimates of Atmospheric Concentrations of Free Radicals and Ozone

Radical	Concentration (1 ppm = 2.4×10^{13} molecules per cubic centimeter)	Location or Source
Hydroxyl	4×10^{-7} ppm at 2.1 km altitude	Four corners (Arizona, New Mexico, Utah, Nevada) ^a
	1×10^{-7} ppm at 6.9 km altitude	Rocky Mountains ^a
	$<1.6 \times 10^{-7}$ ppm to 3×10^{-7} ppm	Kuhr Valley, W. Germany ^b
	4×10^{-8} to 2.5×10^{-6} ppm	Dearborn, Mich. ^c
	10^{-8} to 10^{-7} ppm	Pullman, Wash. ^d
	10^{-7} ppm (Estimate based on data for pollutant loss rates)	November 5, 1973, Los Angeles, Calif. ^e
	$>10^{-8}$ ppm (Yearly average daytime value based on NO_x loss)	Los Angeles, Calif. ^f
	$2-5 \times 10^{-8}$ ppm	Annual daylight average based on chlorofluorocarbon lifetimes in Northern Hemisphere ^g
	3×10^{-8} ppm	Annual daylight average in the troposphere over Northern Hemisphere: Atmospheric photochemical model ^h
	1.5×10^{-7} ppm	Summer noon value at ground level. Atmospheric photochemical model ^h
Atomic Oxygen	$\frac{k_{17}[\text{NO}_2]}{k_{18}[\text{O}_2]} \cong 3 \times 10^{-9}$ ppm, where $\text{NO}_2 = 0.1$ ppm	Calculated from Reactions 17 and 18 below in text
Ozone	Typically varies between 0.001 and 0.5 ppm in sunny, heavily polluted areas	See Figure 4-9 ⁱ
	Background clean air contains $\cong .030$ ppm ozone.	Northern Hemisphere ^j
Peroxy	$\leq 10^{-4}$ ppm	Computer estimate ^k

^aDavis et al., 1979.

^bPerner et al., 1976.

^cWang et al., 1975.

^dCampbell et al., 1979.

^eCalvert, 1976.

^fChang et al., 1979.

^gSingh, 1977.

^hCrutzen and Fishman, 1977.

ⁱU.S. Environmental Protection Agency, 1978.

^jSingh et al., 1978.

^kHendry, 1979.

TABLE 4-6. Rate Constants for Reactions of Toluene with Reactive Species in the Atmosphere^a

Species	Estimated Average Daytime Annual Concentration, ppm	Rate Constant, ppm ⁻¹ min ⁻¹	Rate of Toluene Removal, ppm/min	Fraction of Toluene Reacted
Hydroxyl radical	4×10^{-8}	9.5×10^3	3.7×10^{-4}	
Atomic oxygen	3×10^{-9}	1.1×10^2	3.3×10^{-7}	
Ozone	3×10^{-2}	5×10^{-7}	1.5×10^{-8}	
Peroxy radical	1×10^{-4}	2.5×10^{-7}	2.5×10^{-11}	

^aModified from Hendry, 1979. These relative rates would be approximately correct for the xylenes and higher alkyl benzenes. An exception is styrene, which reacts rapidly with ozone due to the presence of the double bond.

which are a function of solar intensity and are zero at night, will determine the chemical lifetime of atmospheric toluene and of the other alkyl benzenes as well. The major exception to this rule is styrene, which will react with ozone at an appreciable rate due to the presence of the vinyl group on the side chain.

Table 4-7 lists the measured rate constants for the reaction of the hydroxyl radical with many of the alkyl benzenes in the atmosphere. Calculations of chemical lifetimes are then based upon an estimated daytime hydroxyl concentration of 4×10^{-8} ppm or 1×10^6 molecule/cm³. This concentration is the best estimate for an annual average, but the actual daily values may vary by as much as a factor of 10 upward or a factor of 50 or more downward, depending upon the local solar intensity, temperature, and composition of trace gas chemicals of the air. The lifetime applies to daylight hours only since the concentration of hydroxyl radicals falls to zero during the night. This variation in concentration carries over directly into the chemical lifetime of any species removed by this radical. Thus, an annual average lifetime has considerable uncertainty and might be totally inapplicable to conditions such as those found at northern latitudes in winter, when longer lifetimes would be expected, or in summer, when much shorter lifetimes would be expected. For example, Calvert (1976) has suggested a value 2.5 times higher than this average for a summer day in Los Angeles. A model developed by Crutzen and Fishman (1977) produces a summer noon ground level value approximately 5 times the average. A more detailed discussion of the atmospheric lifetime is presented below.

Reaction Products and Mechanisms

Although the relevant rate constants for the reaction of alkyl benzenes with the hydroxyl radical have now been measured extensively (Atkinson *et al.*, 1978), the overall mechanism of the attack and the intermediate and final reaction products are largely unknown and represent one major area of uncertainty about urban atmospheric photochemistry (Herron *et al.*, 1979).

Hydroxyl radicals may react with an alkyl benzene either by abstraction of a hydrogen atom from the side chain or by ring addition. Abstraction of a ring hydrogen does not occur. (In styrene, rapid addition to the vinyl double bond would occur as well.) These processes may be illustrated for toluene as follows:

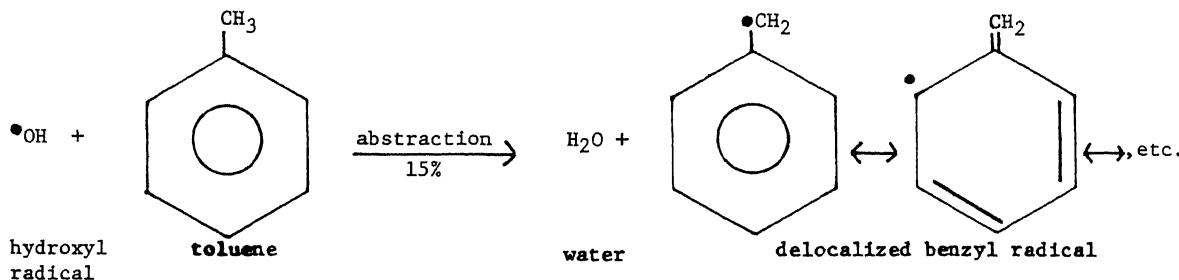


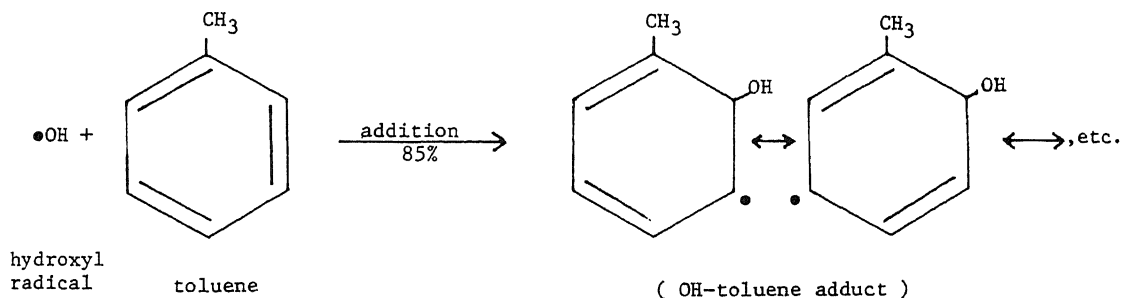
TABLE 4-7. Rate Constants^a and Computed Atmospheric Chemical Lifetimes^b for Benzene and Its Alkyl Derivatives

Compound	Rate Constants, $10^{12} \text{ k cm}^3 \text{ molec}^{-1} \text{ sec}^{-1}$	Chemical Life Daylight Ho
Benzene	1.3	200
Toluene	5.6	50
Ethylbenzene	7.7	35
<u>o</u> -Xylene	14.	20
<u>m</u> -Xylene	22.	12
<u>p</u> -Xylene	12	23
<u>n</u> -Propylbenzene	5.9	50
Isopropylbenzene	6.8	40
<u>o</u> -Ethyltoluene	13.	21
<u>m</u> -Ethyltoluene	18.	15
<u>p</u> -Ethyltoluene	12.	25
1,2,3-Trimethylbenzene	27.	10
1,2,4-Trimethylbenzene	35.	8
1,3,5-Trimethylbenzene	52.	6

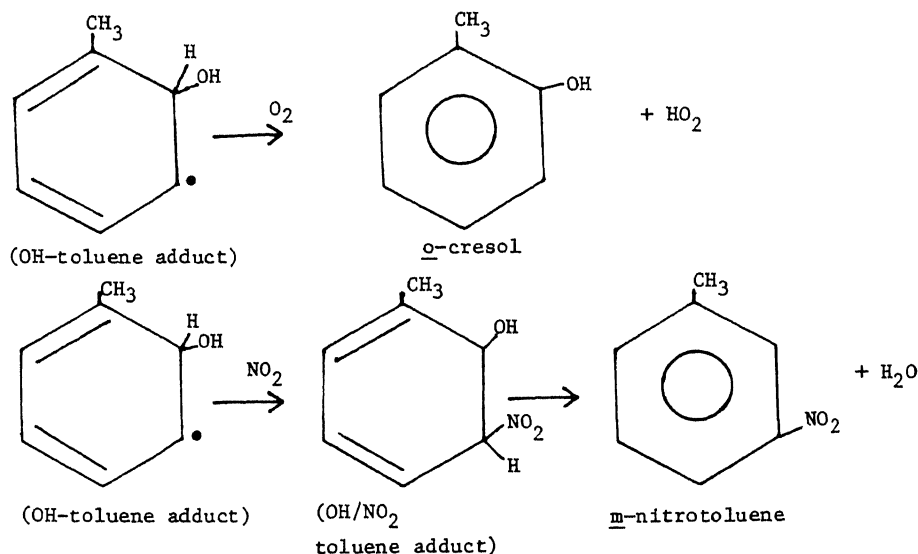
^aUnweighted average of values reviewed by Atkinson et al., 1978.

^bBased on an estimated daylight ambient hydroxyl concentration of 1×10^6 molecules/cm³ (4×10^{-8} ppm). This value is subject to considerable uncertainty and may vary on a day-to-day basis by an order of magnitude up or down, depending on solar intensity, temperature, and local trace gas chemical composition of the atmosphere.

For addition, any position may be attacked. However, the hydroxyl radical adds electrophilically in a fashion similar to oxygen atoms (Grovenstein and Mosher, 1970). Therefore, the ortho addition is preferred.

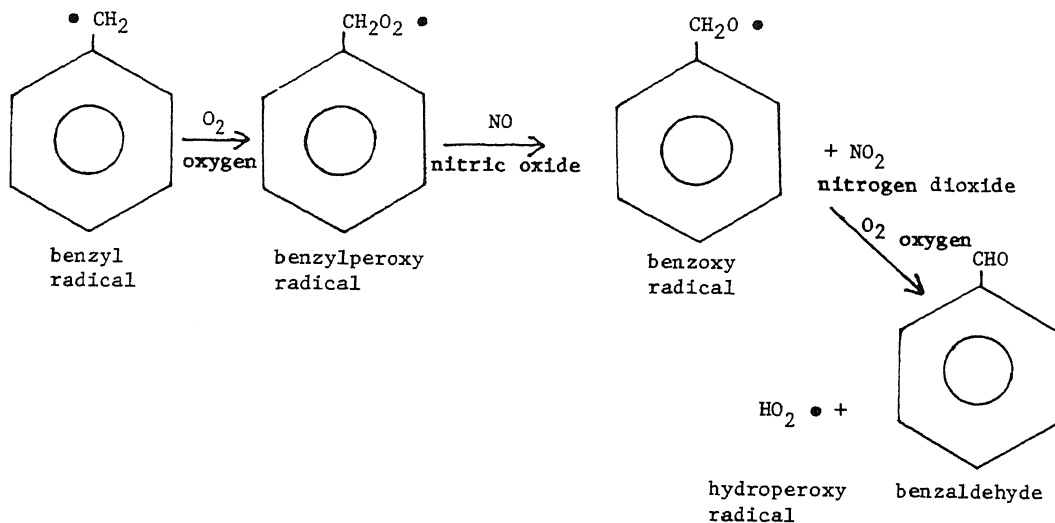


For toluene, the relative proportions for Reactions 1 and 2 have been measured by kinetic analysis (Perry *et al.*, 1977) and by direct measurement of products (Kenley *et al.*, 1978). The subsequent fate of these intermediates is currently in doubt. In one study, conducted at low pressure in a discharge flow system, Kenley *et al.* (1978) identified benzaldehyde, benzyl alcohol, cresol isomers, and nitrotoluene as products and determined their yields. In these experiments nitrogen dioxide and molecular oxygen were present in addition to toluene and hydroxyl radicals. The only isomer of nitrotoluene was the meta-isomer, whose yield varied in proportion to the ratio of nitrogen dioxide to molecular oxygen. Thus, Kenley and his colleagues propose the following mechanism for the addition pathway:



They found the rate constant ratio for these competing steps to be $k_4/k_3 = 4 \times 10^3$. However, at normal atmospheric ratios of nitrogen dioxide to molecular oxygen ($\ll 10^{-6}$), they predict that the relative nitrotoluene to cresol yield would be 1% or less. This agrees with the work of O'Brien *et al.* (1975b), which was carried out under simulated atmospheric conditions that gave approximately 10% yield of nitrotoluene at nitrogen dioxide concentrations of 20 ppm.

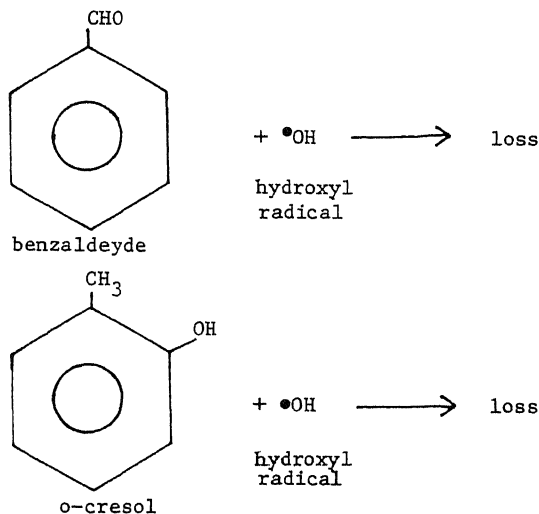
The mechanism for the abstraction pathway following Reaction 1 would be:



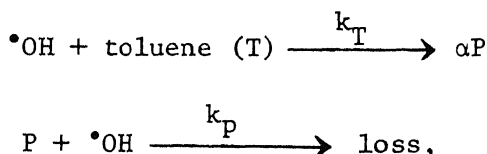
Based on the relative rates of Reactions 1 and 2, Kenley and his colleagues have proposed that the atmospheric reaction of the hydroxyl radical with toluene should yield 15% benzaldehyde and 85% cresol isomers with minor ($<1\%$) amounts of nitrotoluene.

The reaction products formed from toluene under simulated atmospheric conditions have been studied by O'Brien *et al.* (1979e). They found the major gaseous ring addition products of the reaction to be *o*-cresol, *m*- and *p*-nitrotoluene, benzyl nitrate, and benzaldehyde. Ring fragmentation products determined quantitatively were acetylene, acetaldehyde, and acetone, but their yields were much less than 1%. Formaldehyde and formic acid were detected by gas chromatography/mass spectrometry but were not measured quantitatively. Both of these compounds were also found as products of the photo-oxidation of alkyl benzenes in an earlier study (Kopczynski, 1964). The nitrogen-containing products had yields of a few percent in the study conducted by O'Brien *et al.* (1979a), in which concentrations of nitrogen dioxide were approximately 1 ppm. The major products of toluene reactions under simulated atmospheric conditions were *o*-cresol and benzaldehyde, but approximate yields were lower than those obtained by Kenley *et al.* (1978) in experiments with a flow tube. Benzaldehyde was one-third to one-half of the 15% reported by Kenley, and *o*-cresol was lower by a factor of approximately 10.

Subsequently, O'Brien *et al.* (1979c) obtained more quantitative data on cresol and benzaldehyde. The yield of each compound following the attack of hydroxyl radical on toluene was found to be approximately 1. In this study, the formation and decay of both products were followed over several toluene lifetimes. Analysis of the data on the product produced both the direct yield of each product in the primary reaction with hydroxyl radical and the rate constant ratios $k_6/(k_1 + k_2)$ and $k_7/(k_1 + k_2)$ for the product loss reactions:



In this analysis, the following mechanism was used:



where P is any product formed with yield α , and k_T and k_P are the rate constants. The resultant rate expressions for change of concentrations (indicated by brackets) with time, t , are:

$$\frac{d[T]}{dt} = -k_T[T][\text{OH}]$$

$$\frac{d[P]}{dt} = -k_P[P][\text{OH}] + \alpha k_T[\text{OH}][T]$$

Dividing Equation 11 by Equation 10 eliminates both time and concentration of hydroxyl radicals as variables:

$$\frac{d(P)}{d(T)} = -\alpha + \frac{k_P[P]}{k_T[T]}$$

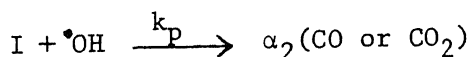
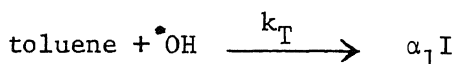
The integrated form of the equation is:

$$\frac{[P]}{[T]} = \frac{\alpha}{R-1} \left[1 - \left(\frac{[T]}{[T]_0} \right)^{R-1} \right]$$

where the rate constant ratio $R = k_p/k_T$. Figures 4-2 and 4-3 show some typical results of O'Brien *et al.* (1979c) for benzaldehyde and *o*-cresol, respectively. These data are plotted according to Equation 13 as a function of the reactant toluene concentration. By fitting Equation 13 to the data, one can determine the value of both R and for each product.

The data for *o*-cresol in Figure 4-3 deviate from the behavior predicted at toluene concentrations less than 6 ppm. This rapid decay of *o*-cresol concentration to a very low level for the remainder of the experiment coincides with the appearance of ozone as a product. When no ozone is formed, the data follow the curve throughout the experiment. This phenomenon is discussed below in the section on aerosol formation.

Average rate constant ratios of 2.3 for benzaldehyde:toluene and 6.0 for *o*-cresol:toluene were in excellent agreement with direct measurements of the individual rate constants (Atkinson *et al.*, 1978 and Niki *et al.*, 1978, respectively). In addition to these two products, O'Brien *et al.* (1979c) determined yields of carbon monoxide and carbon dioxide formed as secondary products in a hypothetical two-step process:



where I is an indeterminate, intermediate product. The product yields are given by α_1 and α_2 . A kinetic analysis of Equation 14 and 15 yields the equation:

$$[\text{CO}_2] = \frac{\alpha_1 \cdot \alpha_2 R}{R-1} \left[\Delta[T] + \frac{[T]}{R} \left\{ \left(\frac{[T]}{[T]_0} \right)^R - 1 \right\} \right]$$

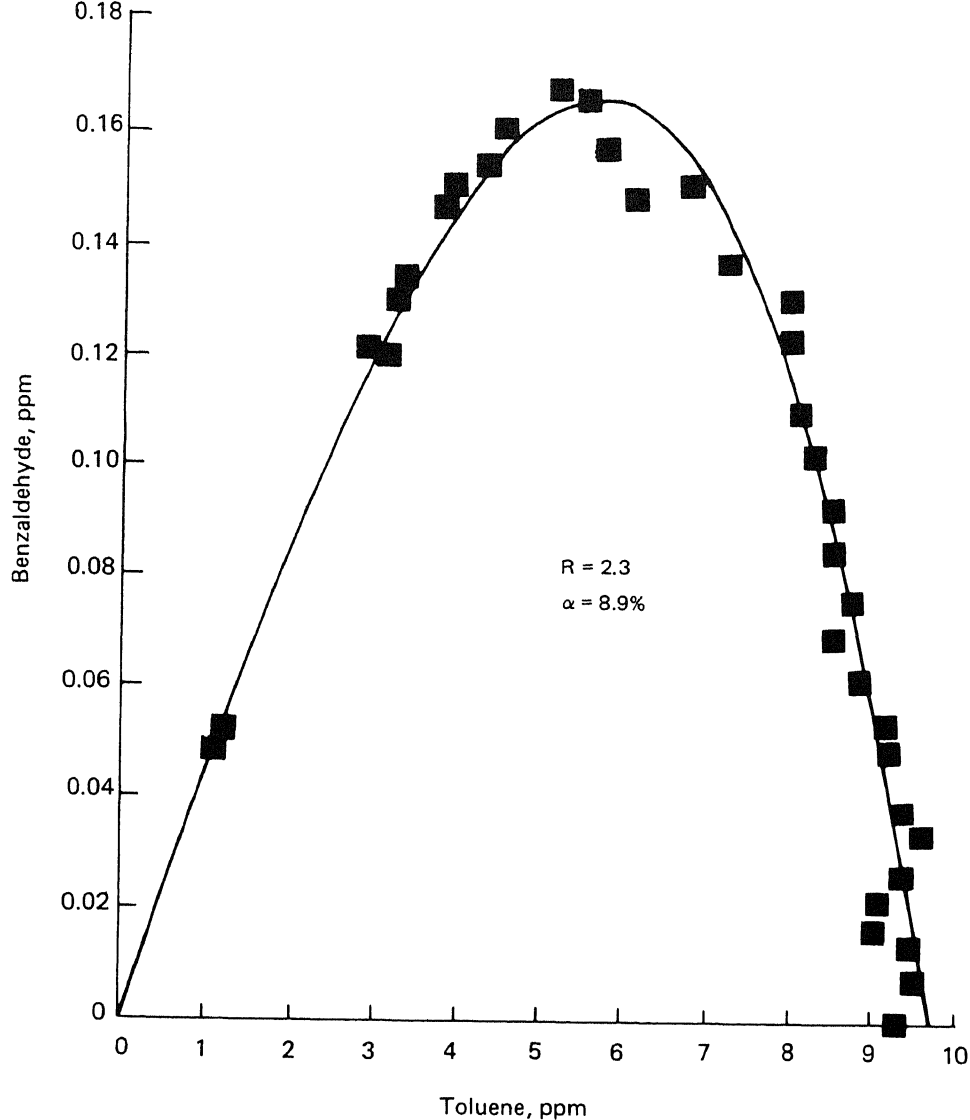


FIGURE 4-2. Reaction of toluene to produce benzaldehyde under simulated atmospheric conditions. Benzaldehyde is plotted against concurrent toluene concentration. (Points are experimental data.) Curve is generated from Equation 13 by optimizing the values of R and α to fit the data. From O'Brien *et al.*, 1979c. ppm = parts per million by volume.

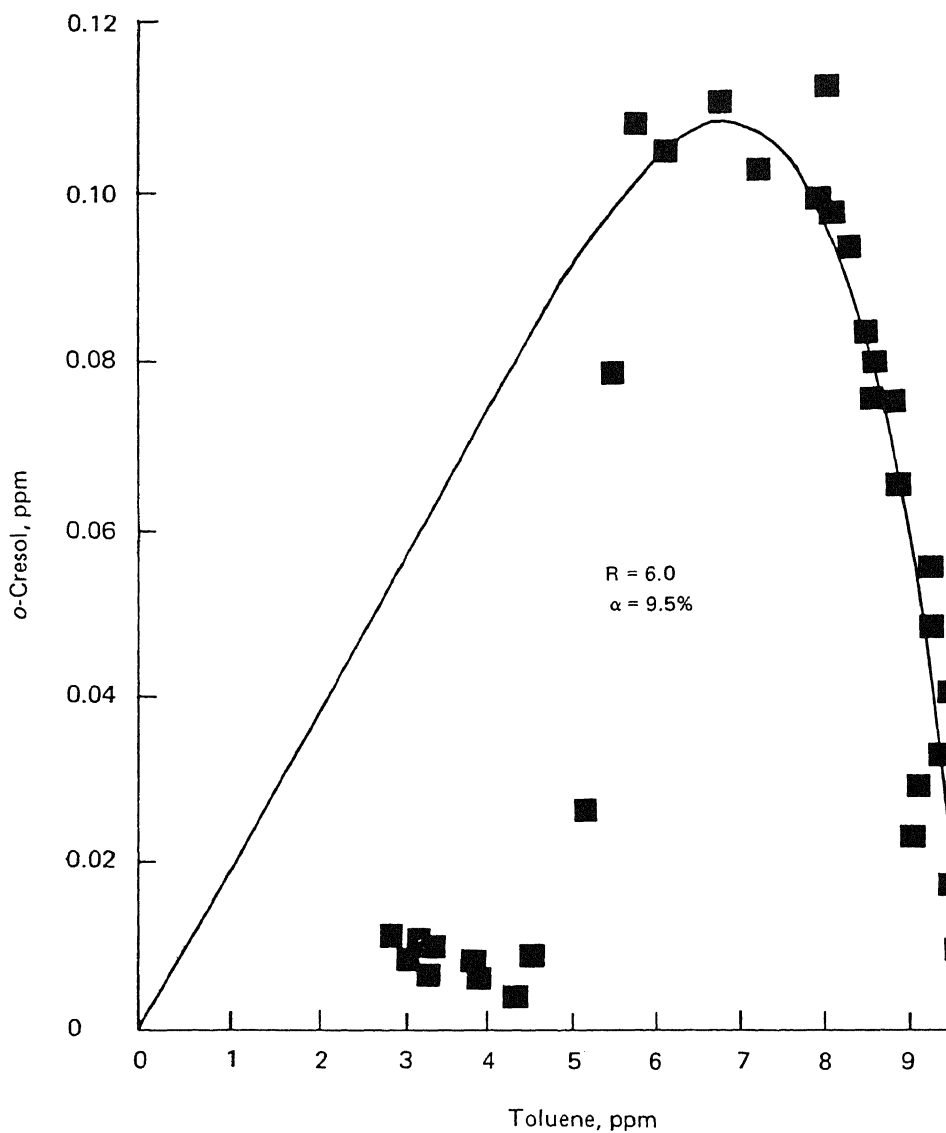


FIGURE 4-3. o-Cresol plotted as a function of toluene concentration in a fashion similar to Figure 4-2. The data deviate from the curve when toluene falls below approximately 6 ppm. This deviation coincides with ozone formation and is discussed in the text. From O'Brien et al. 1979c.

This equation describes the formation of carbon dioxide from toluene as a function of the relevant yields and rate constants in Reactions 14 and 15. It also applies to carbon monoxide, which is oxidized to carbon dioxide by hydroxyl radicals in a much slower reaction. Figure 4-4 shows the data of O'Brien et al. (1979c) for carbon monoxide and carbon dioxide plotted according to Equation 16. This analysis is not unique as it is for Equation 13 since several products with different R values may break down to form carbon monoxide and carbon dioxide. Thus, the actual values of R and $\alpha_1 \cdot \alpha_2$ are probably composites. The investigators found carbon monoxide yields of 15% and carbon dioxide yields between 18% and 40%, expressed as $\alpha_1 \cdot \alpha_2$. The intermediate products broke down to form carbon monoxide and carbon dioxide by reacting with hydroxyl radicals 2 to 3 times faster than does toluene. For benzaldehyde and o-cresol, photodissociation does not seem to be an important pathway. For the intermediate products, photolysis would be included in the apparent value of R. In these experiments, a combustion technique, which was used to measure total gas phase carbon, showed that 60% of the reacting toluene left the gas phase and deposited on the walls of the reaction vessel. Subsequently, the products on the walls and/or their equilibrium vapor phase components broke down very slowly to yield carbon monoxide and carbon dioxide. After several weeks, a balance of gas phase carbon was again established. In particle-free air, the 60% gas phase deficit was produced without generating sufficient supersaturation to cause homogeneous nucleation of any aerosol particles.

O'Brien et al. (1979c) conducted experiments in a 15-m³ Teflon chamber exposed to sunlight, which yielded similar gas phase products of cresol and benzaldehyde. Aerosol yields were determined by filtration and by a piezo-electric mass balance. These yields ranged from normal results of a few percent to a high of 10%, despite the presence of ambient concentrations of preexisting particulate matter, which could serve as seed nuclei. Thus, even in the presence of ambient aerosols in a fairly large containment vessel, most of the products of the oxidation of toluene do not form aerosol but must deposit on the walls of the reaction vessel.

The investigators measured the vapor pressure of the limited amount of aerosol that was formed and collected on a filter. At 25°C, the pressure was approximately 0.5 ppm carbon atoms by volume. The measurement was made by oxidizing the evaporated aerosol to carbon dioxide. Since urban concentrations of toluene would normally range from 10 to 50 ppb (0.07 to 0.35 ppm of carbon), it seems unlikely that these toluene oxidation products would form aerosol under ambient conditions. Vapor pressure of the aerosol that was adsorbed on a Pyrex surface was found to be considerably less than that collected in the bulk phase on a filter. These observations confirmed the

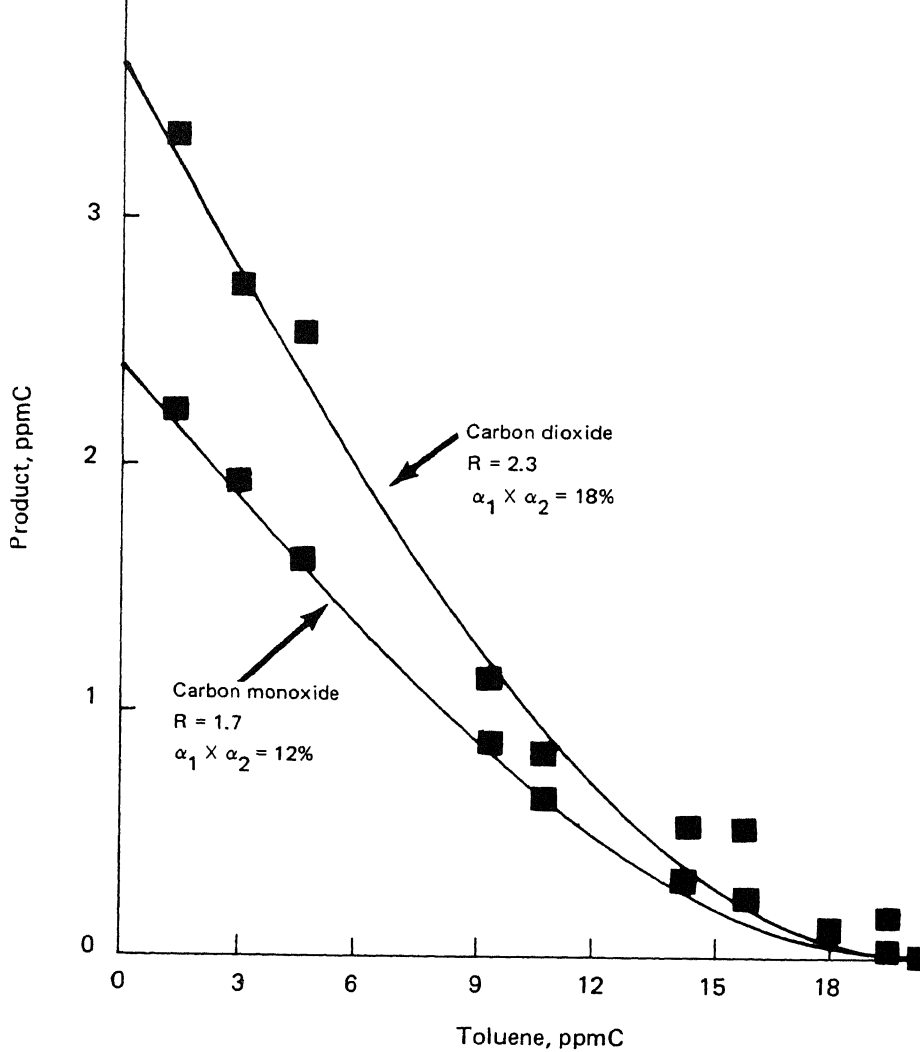
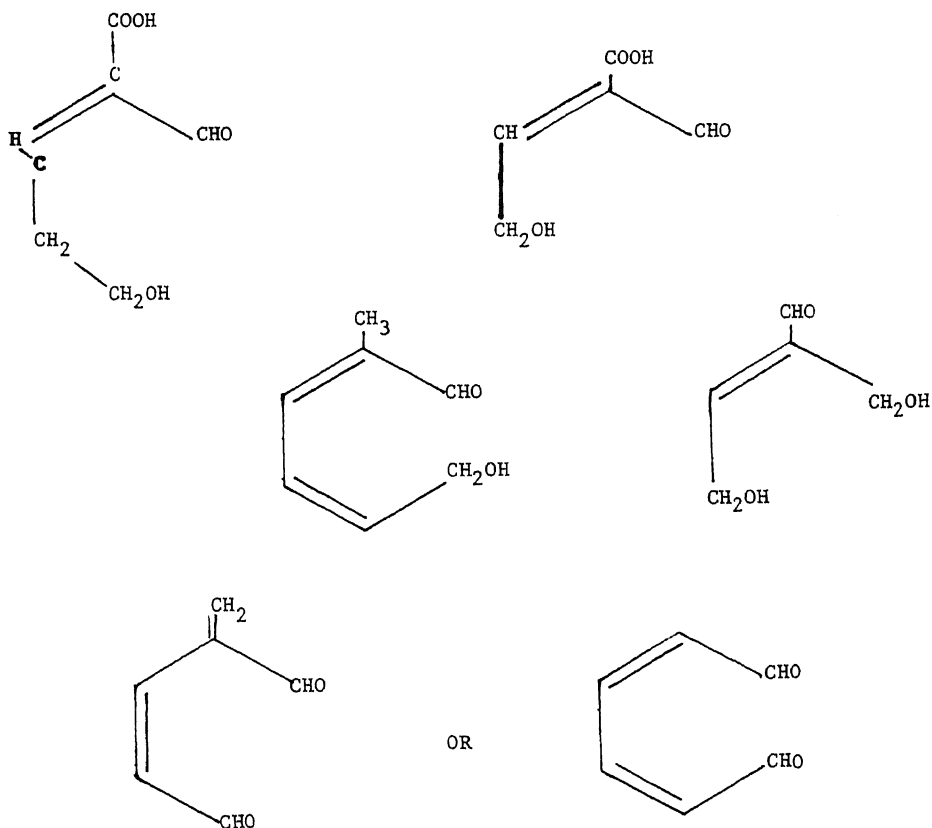


FIGURE 4-4. The formation of carbon monoxide and carbon dioxide from toluene reacting under simulated atmospheric conditions. The curves are generated from Equation 16 by optimizing values of R and α_1 and α_2 . From O'Brien *et al.*, 1979c. Concentration in ppmC, parts per million by volume carbon atoms, e.g., 1 ppm toluene (C_7) = 7 ppmC.

preference of the oxidation products for dry deposition. However, given the relatively low ambient concentration of alkyl benzenes and the relatively high vapor pressure of their intermediate oxidation products, the products in the atmosphere could remain in the gas phase until they break down further, ultimately producing carbon monoxide and carbon dioxide.

The chemical nature of aerosol produced from toluene (at relatively high concentrations such as 10 ppm) under simulated atmospheric conditions has been studied by Schwartz et al. (1974), who identified nitrocresol isomers and ring-opened species such as the following multifunctional, oxidized ring fragments (unsaturated alcohols, aldehydes and acids):



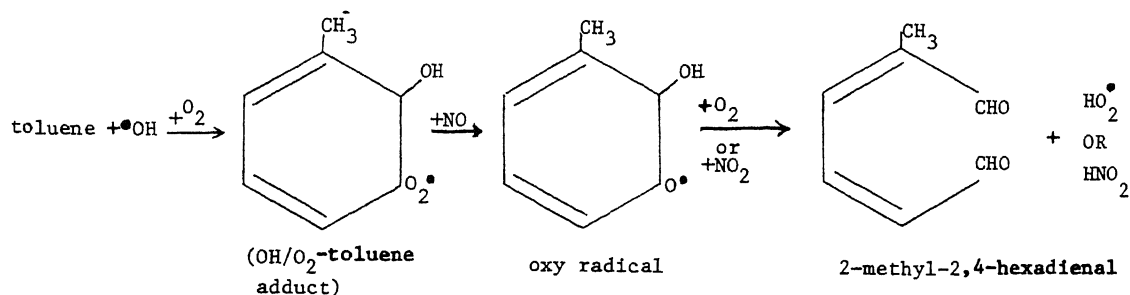
The production of nitro compounds can be explained by the subsequent measurements of Kenley et al. (1978), which were described above. The concentrations of nitrogen oxides (NO_x) used by Schwartz et al. (1974) (2-5 ppm) are from 10 to 100 times higher than typical ambient levels. In ambient air, they would be much less important products than the oxidized ring-opened alcohols, aldehydes, and

acids, which might not exist in the aerosol phase at all, depending on vapor pressure (O'Brien et al., 1975a). However, in the studies of Schwartz et al. (1974), O'Brien et al. (1975a), and similar studies, the formation of aerosol was forced by the use of hydrocarbon concentrations that ranged from 10 to 100 times higher than those found in the environment. This does not necessarily invalidate the product identification, but simply means that the atmospheric products may remain in the gas phase. Compared with their parent alkyl benzene molecule, these products would be expected to react more rapidly with hydroxyl radicals and ozone due to their loss of aromaticity.

The oxidation of benzene, toluene, and ethylbenzene has been studied by Hoshino et al. (1978) who used photolysis of nitrous acid (HNO_2) as a source of hydroxyl radicals. Benzene yielded phenol and nitrobenzene. Toluene yielded cresols, benzaldehyde, m- and p-nitrotoluenes, and benzyl nitrate. Ethylbenzene yielded ethyl phenols, benzaldehyde, acetophenone, and m- and p-nitroethylbenzene. These products resulted from mechanisms similar to those described above. The nitro compounds again formed as a result of the relatively high concentrations of nitrogen dioxide and were found to be roughly proportional to those concentrations. The yield of benzaldehyde averaged approximately 50% that of cresol. Absolute yields were not determined.

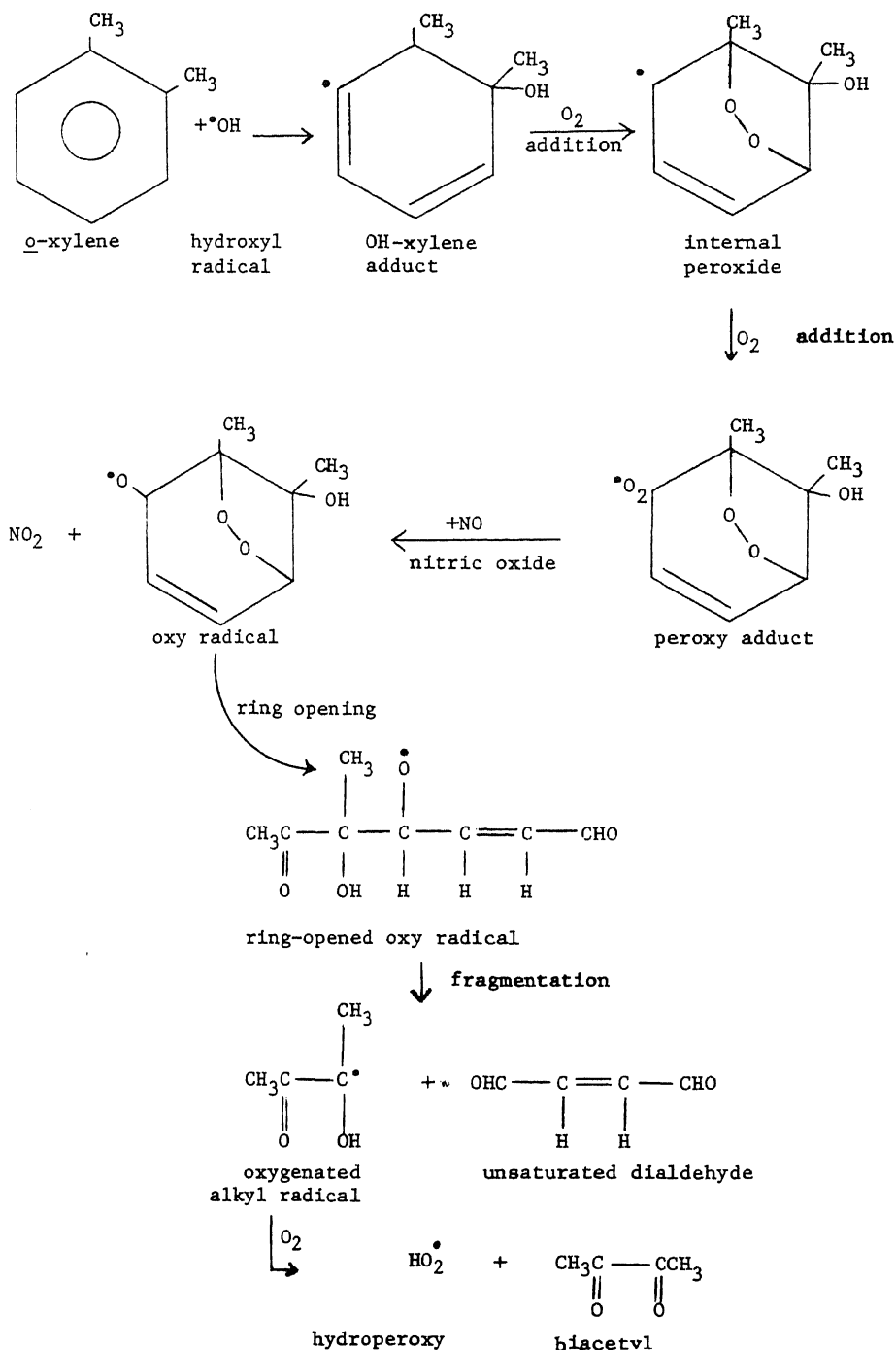
Regarding the major gas phase products, Kenley et al. (1978) reported that the yield of cresol to benzaldehyde was 6:1 in a flow tube study, Hoshino et al. (1978) reported 2:1, and O'Brien et al. (1979d) reported approximately 1:1. The yields of O'Brien et al. (1979d) were determined on an absolute basis by kinetic analysis of the entire toluene decay process. These investigators simulated atmospheric conditions and, more importantly, gave an independent measurement of the rate constant ratios of o-cresol and benzaldehyde to toluene for the reaction with hydroxyl radical. The values are in agreement with independent measurements of the individual rate constants by these investigators.

Hoshino et al. (1978) observed that the reaction of toluene with hydroxyl radicals yielded a product with a mass spectrum suggesting 2-methyl-2,4-hexadienal. They suggested the following mechanism of formation for this product:



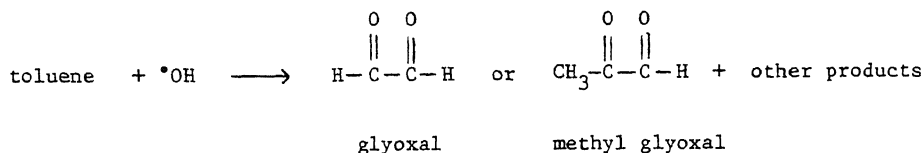
This compound would then compete with o-cresol as the initial product of the hydroxy-toluene adduct. Surprisingly, this dialdehyde was not included in the list of a half dozen similar aerosol products reported by Schwartz et al. (1974).

Darnall et al. (1979) identified biacetyl as a product of the reaction of the hydroxyl radical with o-xylene under simulated atmospheric conditions. Their proposed mechanism involved ring cleavage following the addition of the radical:

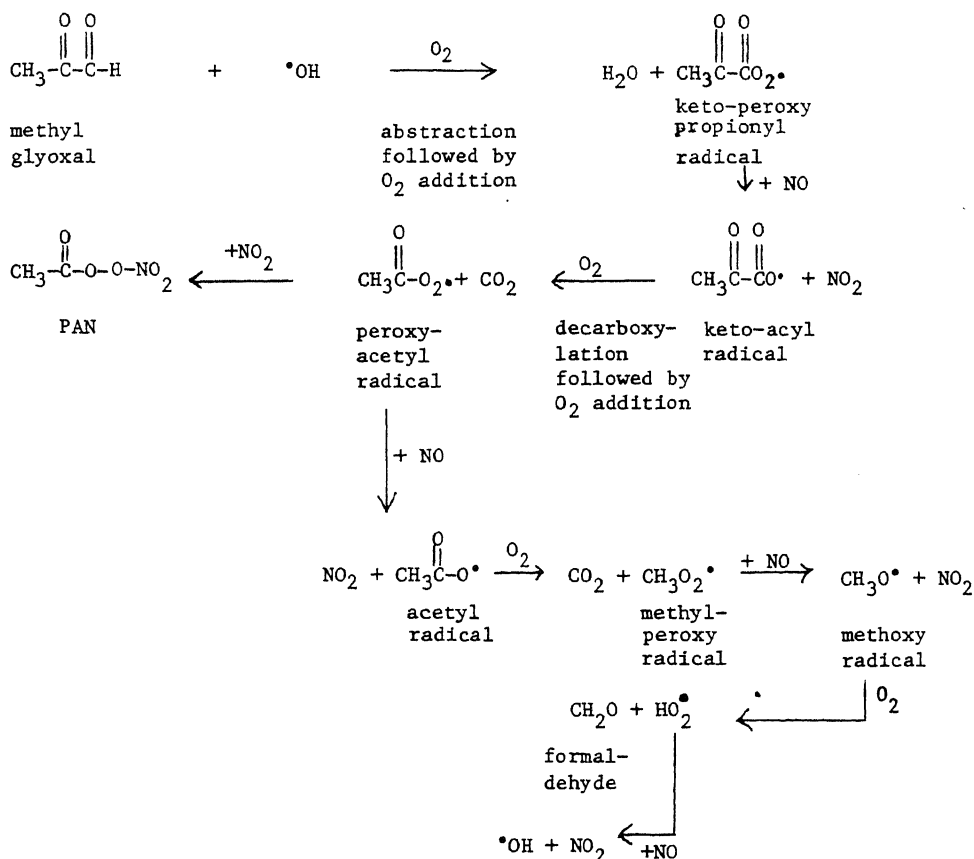


The investigators calculated that 18% of the reaction of hydroxyl radical with o-xylene resulted in the formation of biacetyl.

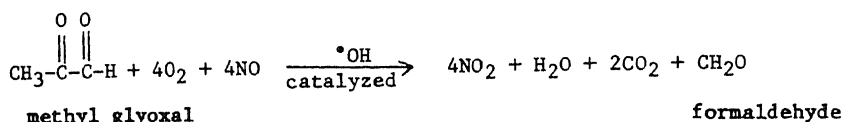
The analogous mechanism for toluene could yield glyoxal or methyl glyoxal:



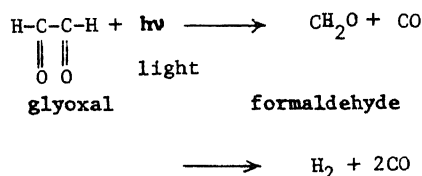
Although this type of compound has not been observed in any study, it seems likely that it is one of the short-lived intermediates responsible for production of carbon monoxide and carbon dioxide as determined by O'Brien et al. (1979c). A likely mechanism for the generation of carbon dioxide would be:



The net reaction in the presence of nitric oxide would be:



Alternatively, photolysis of glyoxal or methyl glyoxal could produce carbon monoxide via several molecular pathways. Calvert and Pitts (1966) discussed the likely mechanism for the photolysis of glyoxal:

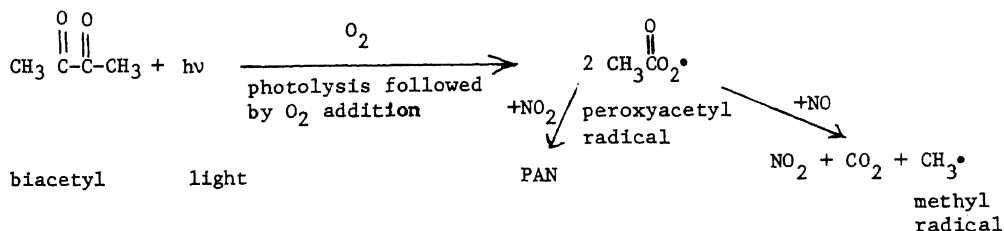


Methyl glyoxal may photodissociate to produce free radicals, although such reactions apparently do not occur with glyoxal at wavelengths greater than 300 nm.

Formation of Peroxynitrates

The recent evidence for ring fragmentation is in agreement with long-standing observations (Altshuller et al., 1971; Heuss and Glasson, 1968; Spicer and Jones, 1977) that toluene and other alkyl benzenes yield a fairly high amount of peroxyacetylnitrate (PAN), a notorious constituent of polluted atmospheres (Stephens, 1969). PAN is formed in high yields from propene, and its production from toluene probably results from either direct fragmentation following reaction with hydroxyl radical or upon secondary reactions of a primary hydroxyl-toluene reaction product.

Possible precursors for the formation of PAN may include some of those discussed in the previous section. Biacetyl, a product of o-xylene (Darnall et al., 1979), photodissociates to form two acetyl radicals, which will form PAN efficiently once photooxidation of nitric oxide (NO) is complete:



Because of the competition between the nitric oxide and nitrogen dioxide pathways in (c) and (d) above, PBzN (like PAN) will accumulate only when nitric oxide has been completely photooxidized to nitrogen dioxide and ozone is present. Even then, PBzN is in equilibrium in the reversible process (d) and will gradually decompose either when it reacts with trace levels of nitric oxide or with peroxy radicals in reaction (e). PBzN is much less stable than PAN, according to measurements of the equilibrium constant for process (d) (D. Hendry, personal communication), and would not accumulate in the atmosphere to the extent that PAN does. It is, however, a much more powerful lacrimator than PAN, even at very low levels. In simulated photooxidation of alkyl benzenes, yields of PBzN and PAN have been reported to range from 0 to 5% for PBzN and from 5% to 30% for PAN.

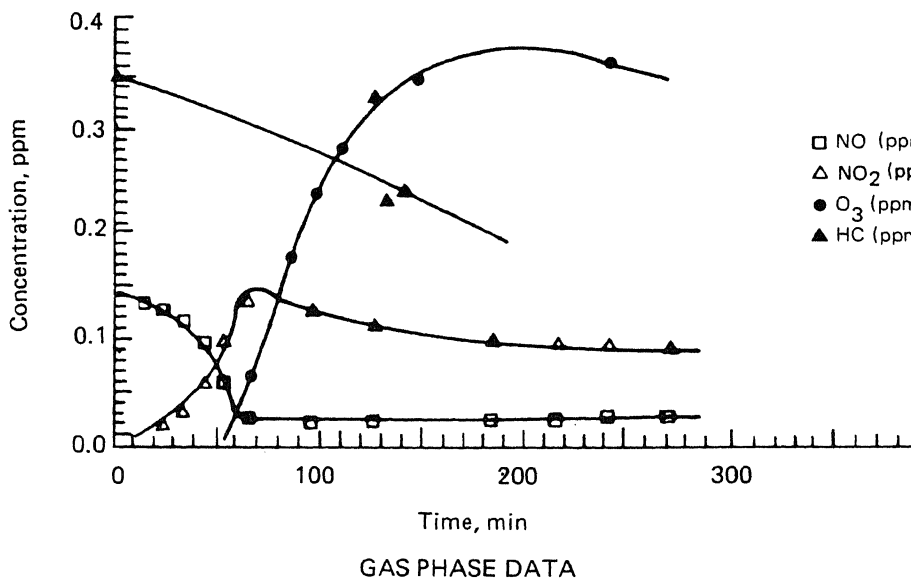
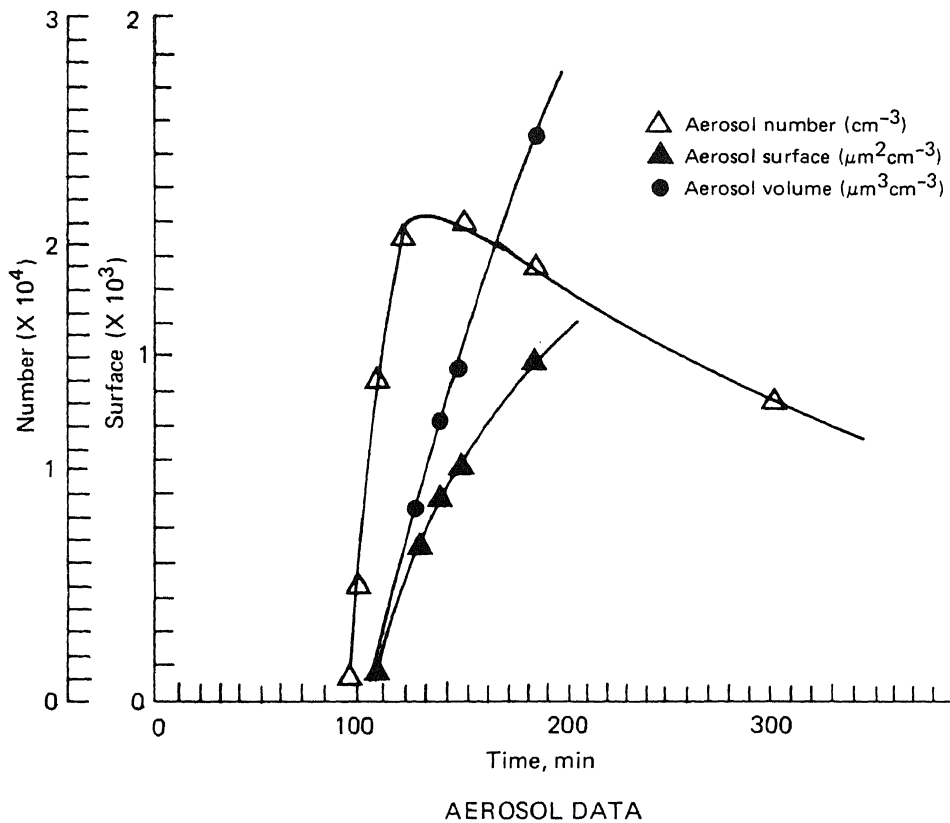
Formation of Aerosol from Alkyl Benzenes

Carbon mass balances in the simulated atmospheric photooxidation of alkyl benzenes have been poor (Gay and Bufalini, 1971; Kopczynski, 1964; Kopczynski et al., 1975). Presumably, most of the oxidation products end up as solids or liquids deposited on the walls of the reaction vessel or condensed to aerosol in the gas phase. Mass balances based on the summation of identified products are always subject to possible error due to undetected products in the gas phase. However, O'Brien et al. (1979c) have confirmed a 60% loss of toluene carbon atoms from the gas phase in simulated atmospheric conditions with toluene at an initial concentration of approximately 3 ppm. They determined total gas phase carbon by passing the air sample over a hot oxidative catalyst and measuring the carbon dioxide produced.

Conversely, alkyl benzenes are not prolific formers of light-scattering aerosols as determined by nephelometry. Most investigators studying the photochemical formation of aerosol have used the far more reactive cycloalkenes and dialkenes (Groblicki and Nebel, 1971; Grosjean and Friedlander, 1980; O'Brien et al., 1975a; Ripperton et al., 1972). However, the poor gas phase mass balances for alkyl benzenes found in smog chamber studies, coupled with the high concentration of alkyl benzenes in urban atmospheres, makes them potentially more significant.

Aerosol vapor pressure and the physical dynamics of aerosol formation have been mentioned above for toluene. Although heterogeneous and even homogeneous nucleation does occur at times, much of the aerosol material must deposit from the gas phase directly on the reaction vessel walls, even in a chamber as large as 15 m³.

One particularly intriguing factor in the chemistry of aerosol formation from alkyl benzenes is the existence of an induction period. This is illustrated for the photooxidation of m-xylene in Figures 4-5 and 4-6. The gas phase data presented in these figures are typi-



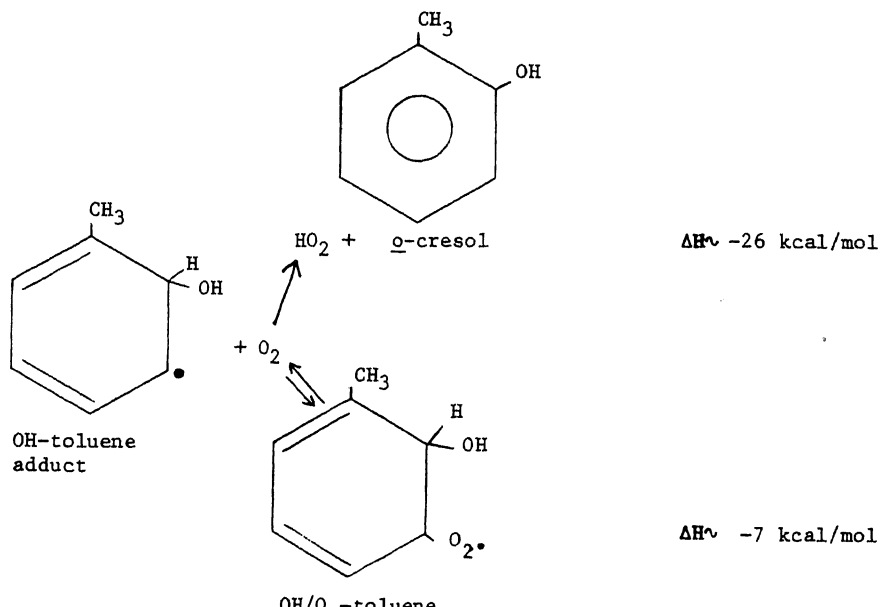
FIGURES 4-5 and 4-6. Aerosol formation in xylene/NO₂ system showing the induction period for aerosol formation. From Kocmond et al., 1975.

before the buildup of ozone while nitric oxide is being photooxidized (see discussion in next section). However, the formation of aerosol entails the same induction period. This is normal for reactions of alkenes, and is usually explained by the fact that alkenes react both with hydroxyl radicals (throughout the course of the reaction) and with ozone (after it is formed). In fact, the disappearance of alkenes accelerates once ozone appears because of the addition of the ozone reaction to the concurrent hydroxyl reaction. Thus, hydroxyl radicals and alkenes do not appear to yield nucleation, whereas ozone and alkenes do. This rationale cannot explain the induction period for alkyl benzenes since they do not react with ozone at an appreciable rate. The alkyl benzenes disappear at a uniform rate throughout the reaction because of their sole removal by hydroxyl radicals. Moreover, although the induction period prevents the nucleation or growth of aerosols, it does not keep the oxidation products of toluene in the gas phase as evidenced by measurements of large carbon deficits during the induction period (O'Brien *et al.*, 1979).

The explanation for this must be that additional new products, which are formed after the induction period, have lower vapor pressures than those formed previously. Thus, nucleation occurs faster than diffusion to the walls can occur.

The induction periods for toluene and xylene coincide with the anomalous disappearance of *o*-cresol (Figure 4-3), which vanishes shortly after ozone appears yet does not react with ozone at an appreciable rate (Atkinson *et al.*, 1978). If ozone does not react with cresol, perhaps the formation of ozone or the disappearance of nitric oxide stops the formation of cresol thereby leading to its disappearance via the hydroxyl reaction.

If one considers the formation of cresol, then molecular oxygen may react either to form cresol by abstracting the α -hydroxyl ring hydrogen or it may add to the ring in a reaction that is more likely to be reversible.



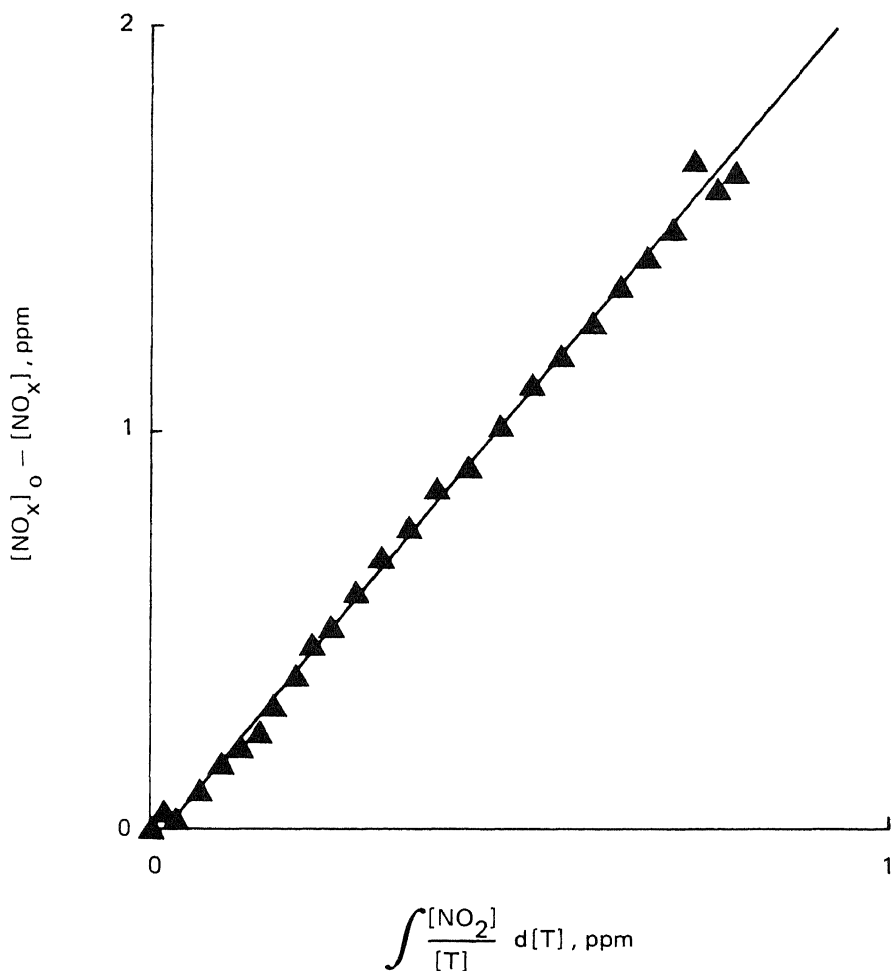


FIGURE 4-7. Plot of NO_x loss in a toluene smog chamber experiment versus the integral $\int \frac{[\text{NO}_2]}{[\text{T}]} d[\text{T}]$.

The linearity and slope indicate all loss of nitrogen dioxide occurs via the reaction: $\text{OH} + \text{NO}_2 \rightarrow \text{HNO}_3$. No ozone was produced in this experiment. From

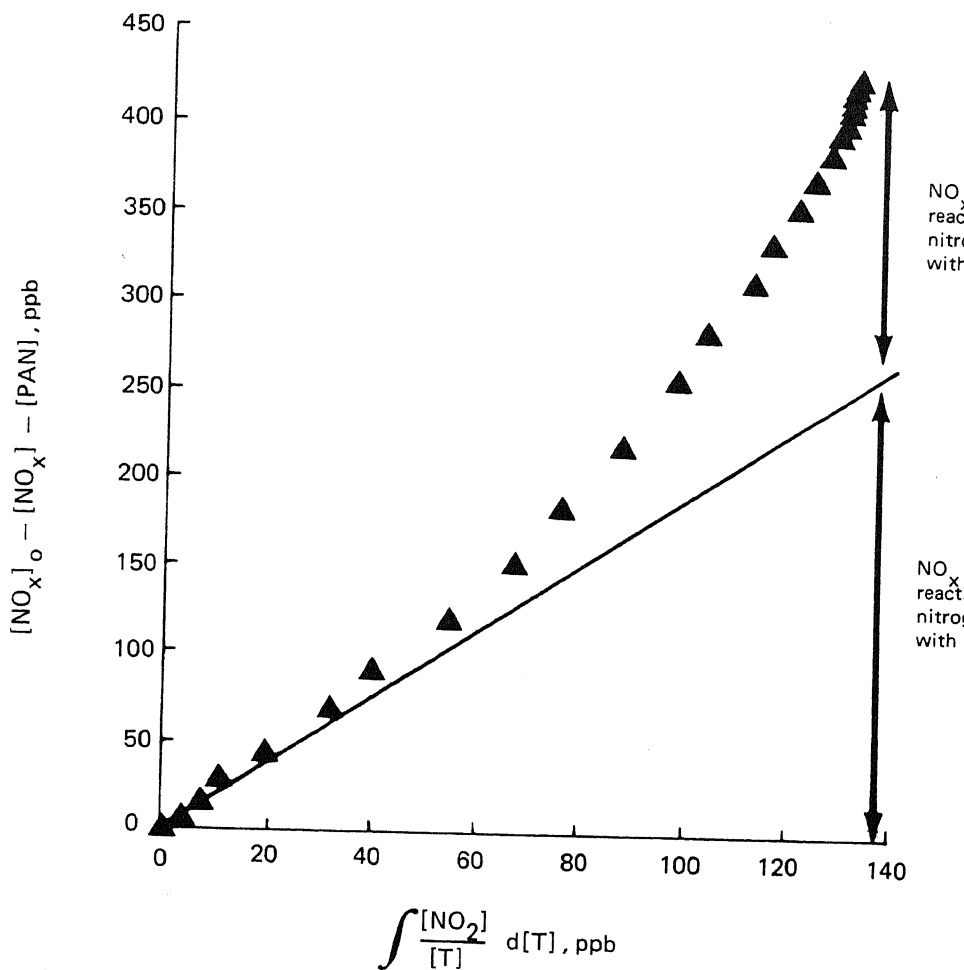
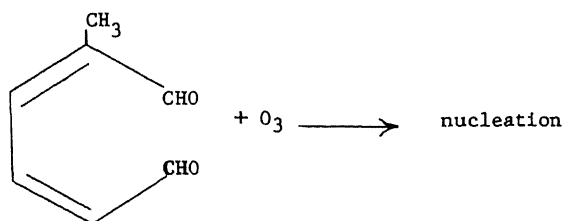


FIGURE 4-8. Plot similar to Figure 4-7 for a reaction that produces ozone. The deviation of data from linearity indicates additional loss of nitrogen dioxide, which correlates with the formation of ozone. The extrapolated line indicates that approximately 250 ppb of nitrogen dioxide reacted with hydroxyl radical and the remaining 150 ppb presumably with ozone to form nitrogen trioxide, which was ultimately lost as well. The formation of PAN, measured NO_x-containing product is taken into consideration in the vertical axis. From O'Brien *et al.*,

2. Cresol, and probably other hydroxy alkyl benzenes, are rapidly destroyed (Figure 4-3).
3. Nitrogen dioxide begins to react to form other products in addition to PAN or nitric acid formed by the hydroxyl reaction (Figure 4-8).
4. Benzaldehyde formation and loss are unaffected (Figure 4-2).
5. Loss of toluene is not accelerated.

A possible explanation is that nitrogen trioxide (NO_3) is formed in the reaction: $\text{NO}_2 + \text{O}_3 \longrightarrow \text{NO}_3 + \text{O}_2$, then reacts with cresol to form aerosol. This explains all of the observed phenomena. However, it is questionable whether the low concentrations of cresol and nitrogen trioxide can have such a large effect on aerosol formation, even if the reaction is very fast.

Another mechanism for autonucleation following the appearance of ozone would involve the reaction of ozone with unsaturated ring-opened fragments formed following hydroxyl addition. For example:



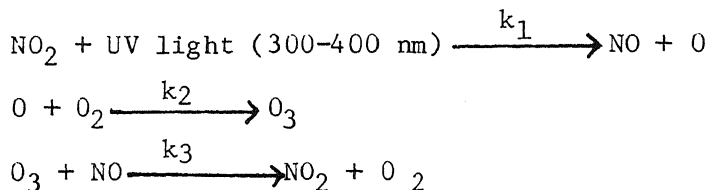
This reaction would be expected to be fast and might produce autonucleation. The pathway would probably have a faster overall rate than a reaction between nitrogen trioxide and cresol, but it is likely that both occur and contribute to the formation of aerosol.

Ozone-Forming Potential of Alkyl Benzenes

The current Federal Air Quality Standard for ozone is 0.12 ppm. Steps required to satisfy this criterion are complex, reflecting the complexity of the photochemical processes involved in the generation of ozone. Very expensive methods of reducing ambient concentrations of hydrocarbons and nitrogen oxide have been proposed or are underway to reduce the levels of ozone formed under sunlight irradiation.

The general mechanisms of ozone formation in polluted atmospheres involves hundreds of reactions (National Academy of Sciences,

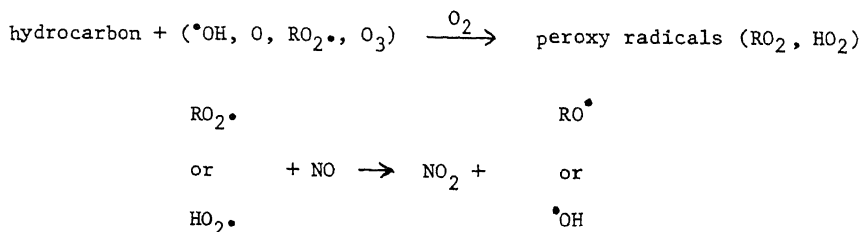
1977). Therefore, only some of the essential features of the process are summarized in this section. Ozone is formed in the troposphere only through the photodissociation of nitrogen dioxide:



Oxygen atoms are efficiently scavenged by atmospheric oxygen to form ozone, which reacts rapidly with the nitric oxide formed in the initial step. These three steps reach a light-induced equilibrium in a few minutes. No further change would be predicted. The concentration of ozone is described kinetically by the photo-stationary equation (Leighton, 1961; O'Brien, 1974; Stephens, 1961):

$$\begin{aligned}\text{O}_3 &= \frac{k_1 [\text{UV light}][\text{NO}_2]}{k_3 [\text{NO}]} \\ &\approx 10^{-2} \text{ ppm} \frac{[\text{NO}_2]}{[\text{NO}]} \quad \text{in bright sunlight}\end{aligned}$$

In early morning air subjected to direct emissions from vehicle traffic and other combustion sources, the ratio of nitrogen dioxide to nitric oxide is normally around 0.2. Thus, the concentration of ozone would be $10^{-2} \times 0.2 = 0.002$ ppm, well below the standard of 0.1 ppm. During the day, however, the ratio increases. Concurrently, the concentration of ozone increases in line with Equation 20. A schematic illustration of idealized behavior is shown in Figure 4-9. As the photooxidation of nitric oxide, ozone begins to accumulate in the afternoon, often reaching concentrations exceeding the Federal Air Quality Standard. This process may be regarded as a perturbation of the "do-nothing" cycle of Reactions 11 through 13 by the process:



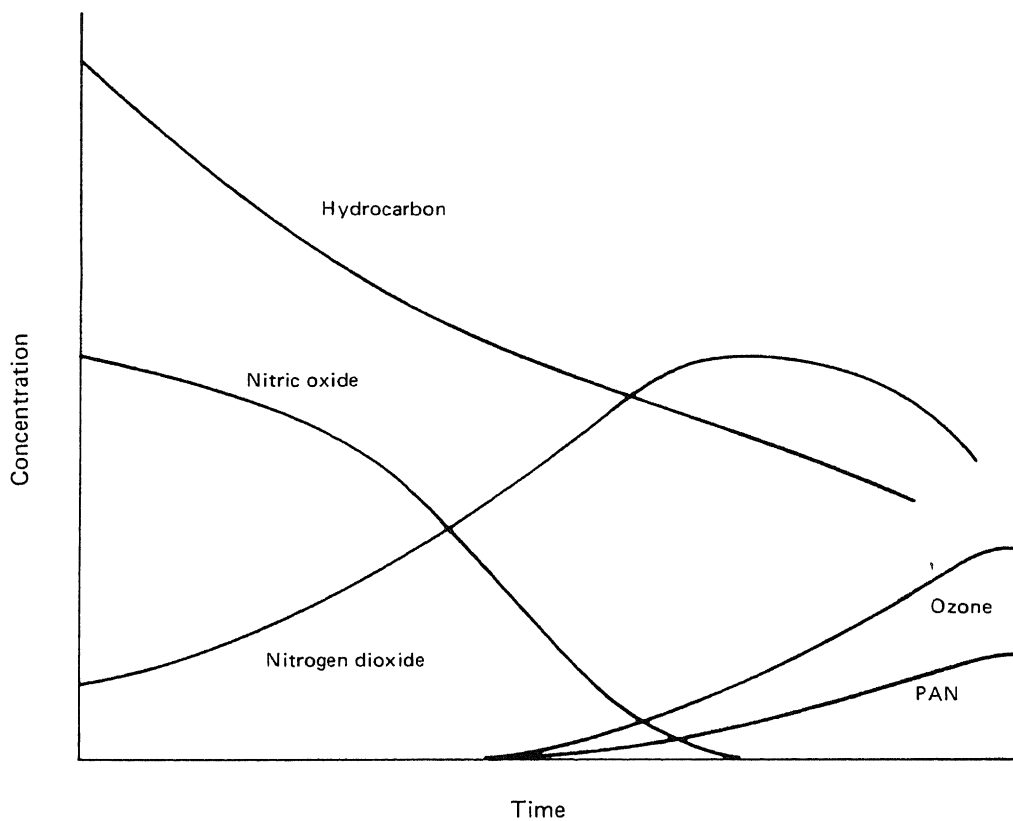


FIGURE 4-9. Typical profile for hydrocarbon-induced photooxidation of nitric oxide, followed by accumulation of ozone.

The oxidation of nitric oxide to nitrogen dioxide is followed by Reactions 17 and 18 to generate an ozone molecule. Nitric oxide is thus photooxidized to nitrogen dioxide. Once this process is complete, ozone begins to accumulate. Thus, oxidant formation is caused by peroxy radicals, which are generated from atmospheric hydrocarbons. Hundreds of individual steps are involved in the reactions of the simple alkanes and alkenes. Studies to determine the steps in the reactions of the alkyl benzenes are in very early stages. The driving force for these reactions is the concentration of trace free radicals, which convert hydrocarbons to hydroperoxyl radicals and peroxy radicals. The species most responsible (almost the sole species for alkanes and alkyl benzenes) is the hydroxyl radical. The process should be described as completely as possible to facilitate the development of cost-effective strategies to control ozone. Because of the ignorance of the relevant chemical processes, current chemical models used for control ignore any contribution from alkyl benzenes. A review of current models for ambient air has been published by the U.S. Environmental Protection Agency (1978).

In the absence of detailed knowledge of the reactions involved in the oxidation of alkyl benzenes and of their contribution to the photooxidation of nitric oxide and the accumulation of ozone, it has been customary to deal with the problem empirically. Traditionally, classes of hydrocarbons and individual hydrocarbons within a class have been characterized by their reactivity in photochemical air pollution.

The reactivity of hydrocarbons may be variously defined by the rate at which nitric oxide oxidizes to nitrogen dioxide, the rate at which ozone forms, the maximum amount of ozone created, the eye irritation produced, etc. Because this subject has been studied extensively by many investigators, no extensive review will be attempted here, although it is critically important to the understanding and control of photochemical air pollution.

However defined, the reactivity of hydrocarbons may be measured in several ways. Individual hydrocarbons may be irradiated and the above-mentioned parameters measured. In this approach the ratio of hydrocarbons to NO_x is of major importance. Often, this ratio is varied during a study of an individual compound. Groups of hydrocarbons may be irradiated in a simulation of atmospheric processes or actual atmospheric air may be irradiated. In either of these approaches, it is difficult to identify the individual contributions of hydrocarbons to overall reactivity, but the rates of photooxidation for each hydrocarbon may provide an indication of the overall participation of a compound in the photochemical process. A final approach is the addition of an individual hydrocarbon to a reference or baseline mixture of representative hydrocarbons of known reactivity followed by an obser-

vation of any increase in reactivity. This procedure offers some advantages over the irradiation of individual hydrocarbons, but may be more difficult to interpret mechanistically.

It is safe to conclude that alkyl benzenes lie in an intermediate position between the reactive alkenes and less reactive alkanes. However, given the relative abundance of the three classes in polluted air (alkanes 55%, alkyl benzenes 35%, alkenes 10%), the aromatics are probably the most important class with respect to reactivity. Therefore, an understanding of their chemistry in the photooxidation process is of extreme importance.

Heuss and Glasson (1968) have studied the reactivity of many hydrocarbons irradiated with nitric oxide. Included among these compounds were a number of alkyl benzenes. These investigators studied the formation rates of nitrogen dioxide and ozone, the consumption of hydrocarbons, the maximum concentration of ozone, and eye irritation index, which, except for eye irritation, were well correlated. They found the general trend of reactivity to be: internal alkenes > multiple alkyl benzenes > terminal alkenes > monoalkylbenzenes > alkanes. When applying these findings to the interpretation of atmospheric processes, one must consider that Heuss and Glasson used all hydrocarbons at an initial concentration of 2 ppm, whereas the concentration of alkyl benzenes in polluted air is roughly 3 times higher than that of alkenes. In addition to their photochemical reactivity, the aromatics have a very high eye irritation index, possibly due to the formation of PBzN and its analogues, which are potent lacrimators.

Kopczynski et al. (1972) have studied the reactivity of ambient air samples from Los Angeles, which were irradiated in plastic bags. They found that the alkyl benzenes were consumed at one-half the rate of the alkenes and that alkanes were consumed at one-fifth the rate, but that alkyl benzenes accounted for the greatest yield of reacted carbon atoms during a 4-hr irradiation. The importance of this class of compounds is apparent, but the high rate of hydrocarbon loss, although indicative of overall reactivity, need not necessarily correlate well with the photooxidation rate of nitric oxide or the yield of ozone.

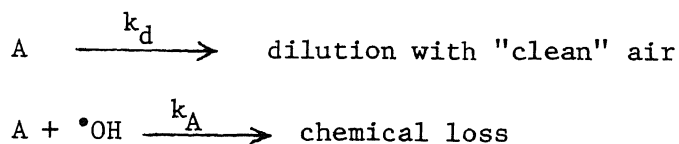
Kopczynski et al. (1975) studied the reactivity of hydrocarbon mixtures containing the three major classes of compounds: the alkyl benzenes, alkenes, and alkanes. They found that the substitution of alkyl benzenes for alkenes resulted in a decrease in oxidant dosage but that eye irritation increased. A further decrease resulted when alkanes were substituted for alkyl benzenes. Alkyl benzenes showed the highest ratio of hydrocarbons consumed to nitric oxide oxidized. This is evidence that the appreciable rates at which hydrocarbons disappear do not necessarily mean high reactivity in the photooxidation of nitric oxide or yield of ozone.

Glasson and Tuesday (1970) have conducted an extensive study of the reactivities of hydrocarbons by irradiating individual hydrocarbons with nitric oxide. Using the photooxidation rate of nitric oxide as a basis, they determined that the alkenes as a class are most reactive, but that some individual alkyl benzenes are even more reactive. The extent of aliphatic ring substitution determines the photooxidation rate of nitric oxide for some alkyl benzenes. The reactivities of the tri- and tetra-alkyl benzenes are similar to those of unsubstituted internal olefins and cyclohexenes; those of the dialkyl benzenes are similar to terminal alkenes. Table 4-8 shows the reactivities of alkyl benzene hydrocarbons as determined by several investigators.

Hendry (1979) and O'Brien et al. (1979c) developed some preliminary mechanisms for the formation of ozone from toluene-induced photooxidation of nitric oxide. However, their studies are in a very early stage of development and require further refinement. Because of the heterogeneity of the chemistry of atmospheric alkyl benzenes, the mechanisms may be quite complex. Nonetheless, they must eventually be understood in order to determine the relationship between ozone and its precursors. Alkyl benzenes are probably the most important contributors to the formation of ozone for short transport times. A specific understanding of the role of each compound in this group is essential to the development of cost-effective controls for emissions of hydrocarbons and nitrogen oxides.

Atmospheric Chemical Removal Processes, Lifetimes, and Reaction Products

As discussed in the first section, atmospheric concentrations of alkyl benzenes are modified by dilution and by chemical reaction with the hydroxyl radical. Only styrene, because of its nonaromatic double bond, reacts appreciably with ozone. Therefore, the ambient concentration of hydroxyl radicals coupled with the hydroxyl-alkyl benzene rate constant will determine the chemical lifetime of an individual molecule. The concentration lifetime will be determined by the sum of the dilution rate constant and the chemical reaction rate constant. Kinetically, this may be expressed by two reactions:



Hydrocarbon	Study				Heuss and Glasson (1963)
	Glasson and Tuesday (1970)	Kopczynski (1964)	Glasson and Tuesday (1970)	Altshuller and Cohen (1963)	
Benzene	1	1	1	1	1
<u>tert-Butylbenzene</u>	1.8				2.8
Isopropylbenzene	2.9	2	5	2	4.1
Ethylbenzene	3.6	2			4.5
Toluene	3.9	2	5	1.3	3.6
1,2-Diethylbenzene	5.2		10	2.7	
1,4-Diethylbenzene	5.2	3	10	2.7	
<u>p-Xylene</u>	6.4	3	10	2.7	4.8
1,3-Diethylbenzene	7.6				
<u>o-Xylene</u>	7.9	3	10	2.7	8.5
3-Ethyltoluene	9.1				
1,2,4-Trimethylbenzene	10	12	17.5	4	
1,2,3,5-Tetramethylbenzene	10.6	20	17.5	6	
<u>m-Xylene</u>	11.2	6	22.5	6.7	9.7
1,2,3-Trimethylbenzene	13.3	12			
1,2,3,4-Tetramethylbenzene	13.6				
1,3,5-Trimethylbenzene	15.5	16	30	8	16.3
Isobutylbenzene					3.1
<u>sec-Butylbenzene</u>					4.8
<u>n-Propylbenzene</u>					3.5
<u>tert-Butylbenzene</u>					3.8

where A is an alkyl benzene and k_d is the rate constant for dilution. The differential and integrated rate expressions are:

$$\frac{d[A]}{dt} = -(k_d + k_A [\cdot\text{OH}]) [A]$$

$$[A] = [A]_0 e^{-(k_d + k_A [\cdot\text{OH}])t} = [A]_0 e^{(-t/\tau)}$$

The lifetime (τ) is the time required for the initial concentration to drop to $1/e$ (the natural number) of its initial concentration or approximately 36% of $[A]_0$. The value of the lifetime is the reciprocal of the first order or pseudo first order rate constant:

$$\tau = (k_d + k_A [\cdot\text{OH}])^{-1}$$

Since dilution only lowers concentrations but does not remove molecules, one usually defines the chemical lifetime as $(k_A [\cdot\text{OH}])^{-1}$. An average value of the atmospheric concentration of hydroxyl radical has been used to calculate the lifetimes for most important atmospheric alkyl benzenes (Table 4-7). The least reactive aromatic compound, benzene itself, has a chemical lifetime of approximately 200 days, 1680 hours, or somewhat more than 2 weeks. The most reactive compound listed, 1,3,5-trimethylbenzene, has a lifetime of only 6 hr. In general, the more substituents on the benzene ring, the more reactive the compound will be with the hydroxyl radical and the shorter its chemical lifetime. The lifetimes themselves are expected to be extremely variable due to variations in the concentration of the hydroxyl radical.

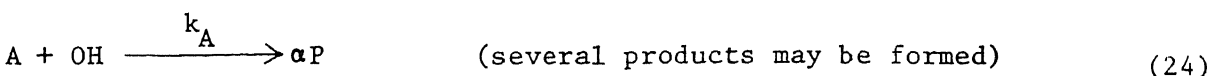
Alkyl benzenes emitted from urban sources move with prevailing winds and undergo chemical reaction concurrently with dilution by cleaner air from aloft or from the sides of an urban or point source plume. The dilution rate will be determined by the local geography and meteorology. Chemical reaction will occur only during the day when the concentration of hydroxyl radical drops to a very low value or at night without sunlight to sustain the free radical reactions in which it is involved. Dilution occurs at identical fractional rates for all gaseous compounds, assuming they all have zero concentration in the "clean" dilution air. Thus, the atmospheric concentration ratio of a pair of compounds will change with residence time in the atmosphere; the less reactive species undergoes a proportionate increase with time.

In the early 1970's, using data from Los Angeles and Toronto, Pilar and Graydon (1973) reported that the ratio of toluene to benzene in urban air was 2.4. At remote locations of the Western United States in 1971, Robinson et al. (1973) collected data on ambient toluene and benzene.

e. From their data, one can calculate that the average ratio of toluene to benzene is 0.25, one may calculate an average air mass residence time that would reduce the toluene:benzene ratio from 2.4 to 0.25. The value calculated is 130 daylight hours, or approximately 5.4 days. Because the geographic history of the air mass is unknown, no significance can be given to this result. However, this demonstrates that lower chemical reactivity can cause a less reactive alkyl benzene to accumulate to a higher level than an alkyl benzene which is more abundant and more reactive species. Benzene, the most persistent compound, would be expected to be the most abundant in remote locations unless natural sources are significant. However, with a chemical residence time of approximately 2 days, even benzene is unlikely to accumulate to any great extent. Unlike highly halogenated hydrocarbons, none of the alkyl benzenes is likely to play an important role in the modification of atmospheric processes.

In the course of reaction with hydroxyl radicals, alkyl benzenes form a variety of intermediate products. These products either remain in the gas phase, where they are ultimately oxidized by free radical processes to carbon monoxide and/or carbon dioxide, or their vapor pressures are so low that they condense to form atmospheric particulate. Ground deposition may occur as well. The relative importance of each pathway has not been adequately studied for the alkyl benzenes. However, using data for toluene, we may draw some conclusions about the two major gaseous atmospheric products and their fates.

Brien *et al.* (1979c) reported that toluene, when subjected to simulated atmospheric conditions, reacts with hydroxyl radicals and yields *o*-cresol and benzaldehyde with yields of approximately 8% each. These two products then react with and are removed by the hydroxyl radical. If we consider an air mass that moves over a pollution source, picks up a hydrocarbon such as toluene, and then moves away from the source, the concentration profile of a reactant hydrocarbon and its products may be analyzed in a fairly straightforward manner:



For simplicity, we have ignored emission source terms, photodissociation of the product or its reaction with ozone radical.

The rate expressions for reactant alkyl benzenes have been given above in Equations 25 and 26. The time-dependent rate expression for product, P, is:

$$\frac{d[P]}{dt} = \alpha k_A [OH][A] - (k_d + k_P [OH]) [P]$$

Dividing Equation 30 by Equation 25 eliminates time as a variable:

$$\frac{d[P]}{d[A]} = \frac{-\alpha k_A [OH]}{k_A [OH] + k_d} + \frac{k_P [OH] + k_d}{k_A [OH] + k_d} \frac{[P]}{[A]}$$

This equation relates the product formation rate to the alkyl benzene disappearance rate. Now if we assume that the concentration of hydroxyl radicals is constant at some average value, we can integrate Equation 31 to obtain the dependence of product concentration on the concentration of parent alkyl benzenes. The result is:

$$\frac{[P]}{[A]} = \left(\frac{\alpha}{R-1} \right) \left\{ 1 - \left(\frac{[A]}{[A]_0} \right)^{\left(\frac{R-1}{L+1} \right)} \right\}$$

For simplicity, we define $R \equiv \frac{k_P}{k_A}$ (rate constant ratio of product to the alkyl benzene reacting with hydroxyl) and $L \equiv \frac{k_d}{k_A [OH]}$ (the ratio of dilution rate constant to chemical reaction rate constant for the reactant).

Figure 4-10 contains a plot of the expected product concentration for benzaldehyde formed from toluene in the atmosphere. For this compound, the ratio $k_P:k_A$ is equal to 2.3, and the yield is 0.1 (O'Brien et al., 1979c). Several curves are plotted for various values of the variable L. If L is zero, no dilution occurs and the product reaches its highest concentration. If L is high, the

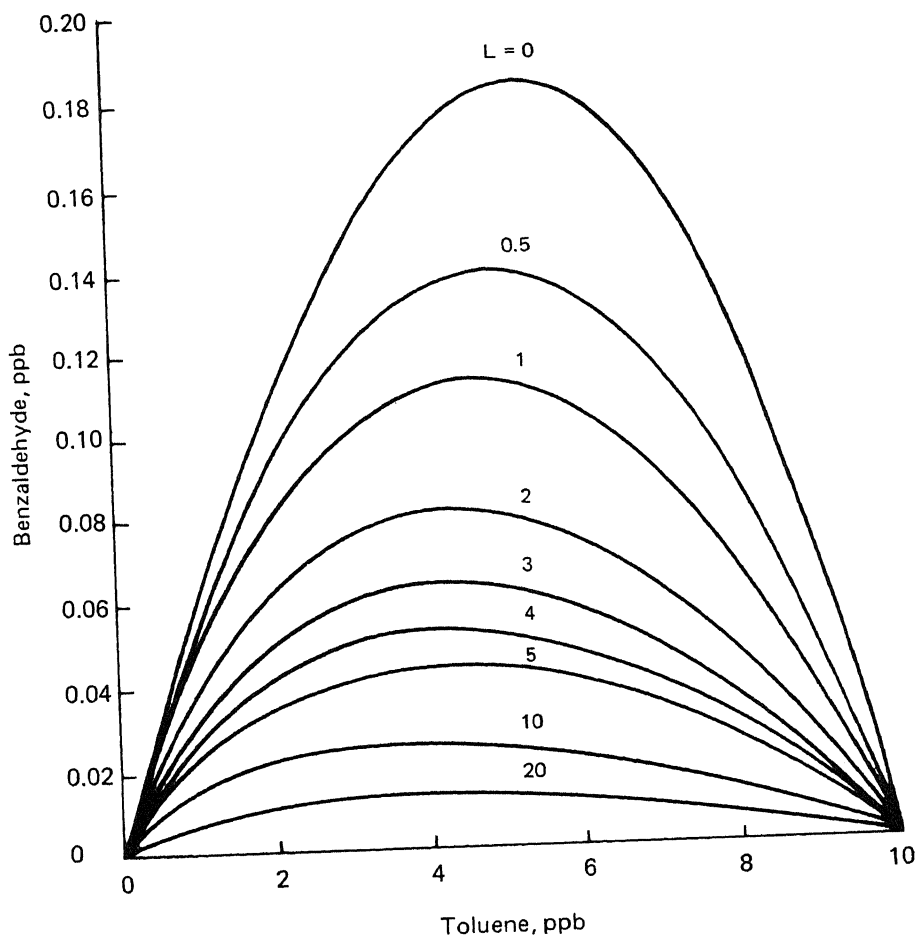


FIGURE 4-10. Concentration of benzaldehyde as a function of reactant concentration for various values of dilution parameter L (Equation 33).

chemical reaction is unimportant and little product is formed. would occur at night or whenever the concentrations of hydroxyl radicals are low. Figure 4-11 provides similar projections for other major gas phase product, o-cresol, which reacts 6 times faster with the hydroxyl radical than with toluene and also has a yield

The maximum concentration of an atmospheric product can be found by setting the derivative of Equation 31 equal to zero, and substituting the resultant equation into Equation 32 to eliminate P.

Two results are obtained. The first gives the maximum concentration as:

$$P_{\max} = \left(\frac{\alpha[A]_0}{R + L} \right) \left(\frac{L + 1}{R + L} \right) \left(\frac{L + 1}{R - 1} \right)$$

where R is the rate constant ratio and L is the dilution ratio. The second gives the time required for this maximum concentration to be achieved in terms of the reactant lifetime, τ , as defined in Equation 27:

$$t_{\max} = \tau \left(\frac{L + 1}{R - 1} \right) \ln \left(\frac{R + L}{L + 1} \right)$$

Plots of each function are given in Figures 4-12 and 4-13 for benzaldehyde and cresol formed from toluene. As the relative rate of reaction increases (increasing L), then less product is formed and it takes longer to reach its maximum concentration.

Equations 34 and 35 are valid within the stated approximations for any hydrocarbon that reacts only with the hydroxyl radical to produce one or several products which themselves react only with hydroxyl radical. If the product photodissociates or there is a continuous emission of the parent hydrocarbon or product itself, then the equations can be expanded with some increase in complexity. If

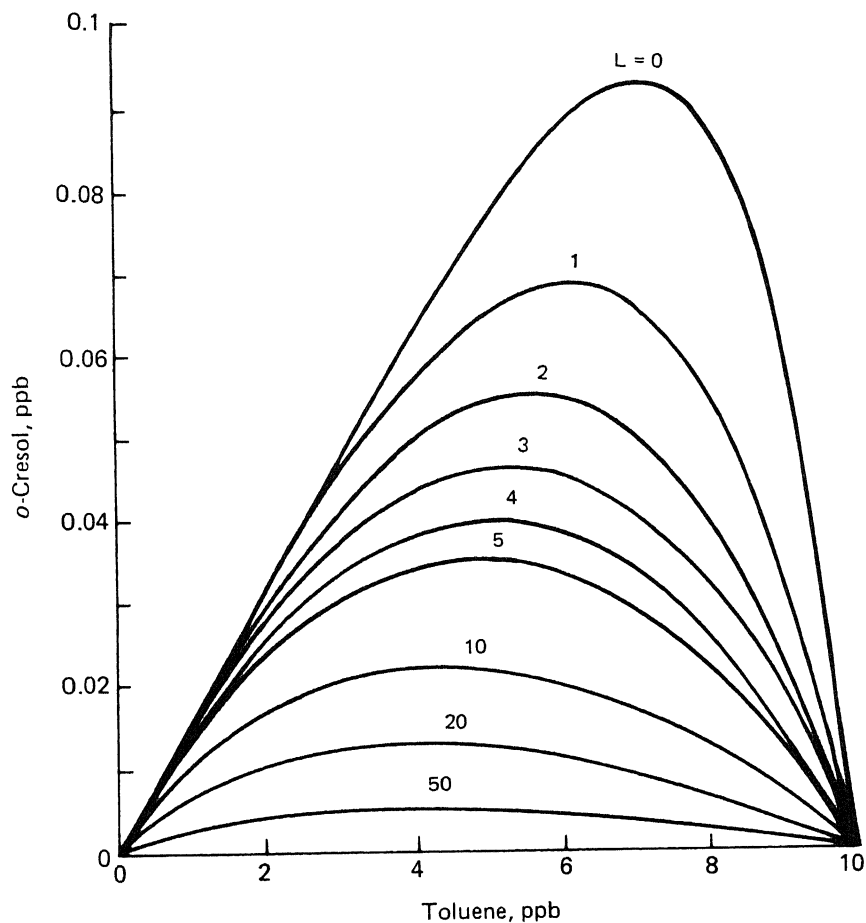


FIGURE 4-11. Concentration of *o*-cresol as a function of reactant concentration for various values of dilution parameter L (Equation 33). However, once ozone forms, cresol rapidly disappears, so these curves would be valid only in the absence of ozone.

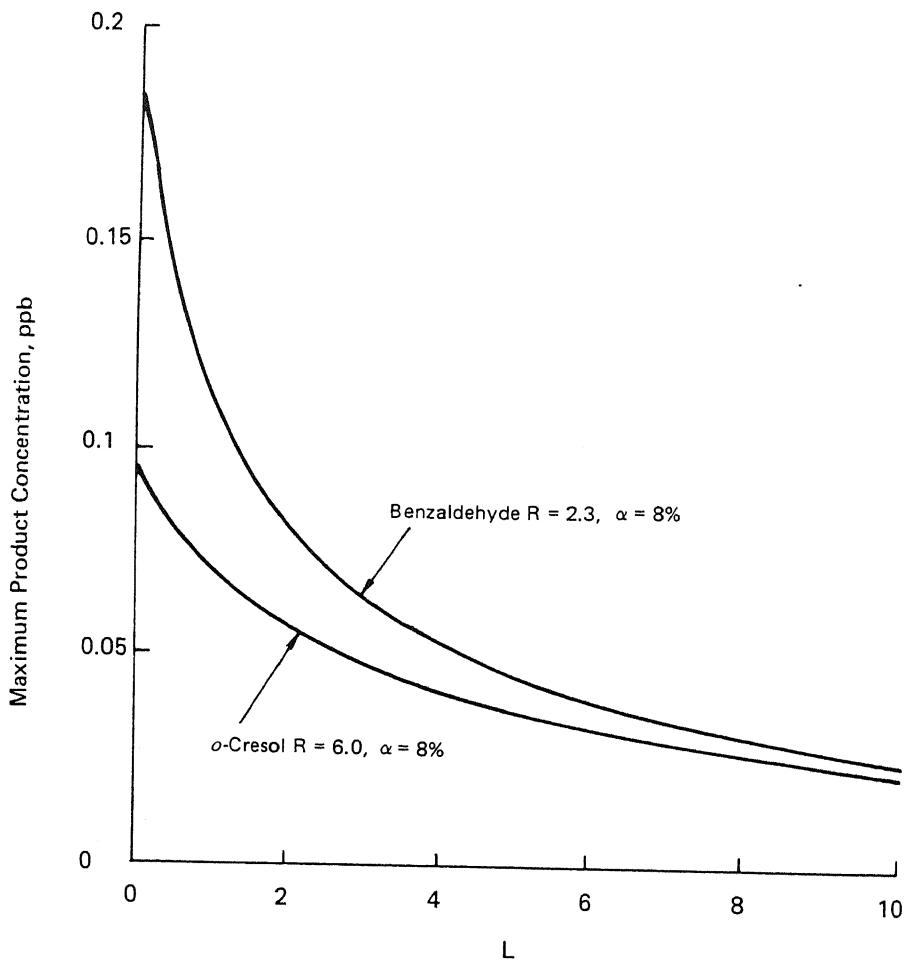


FIGURE 4-12. Maximum product concentration (Equation 33) as a function of dilution parameter L for an initial toluene concentration of 10 ppb. This equation is invalid for o-cresol if ozone is present.

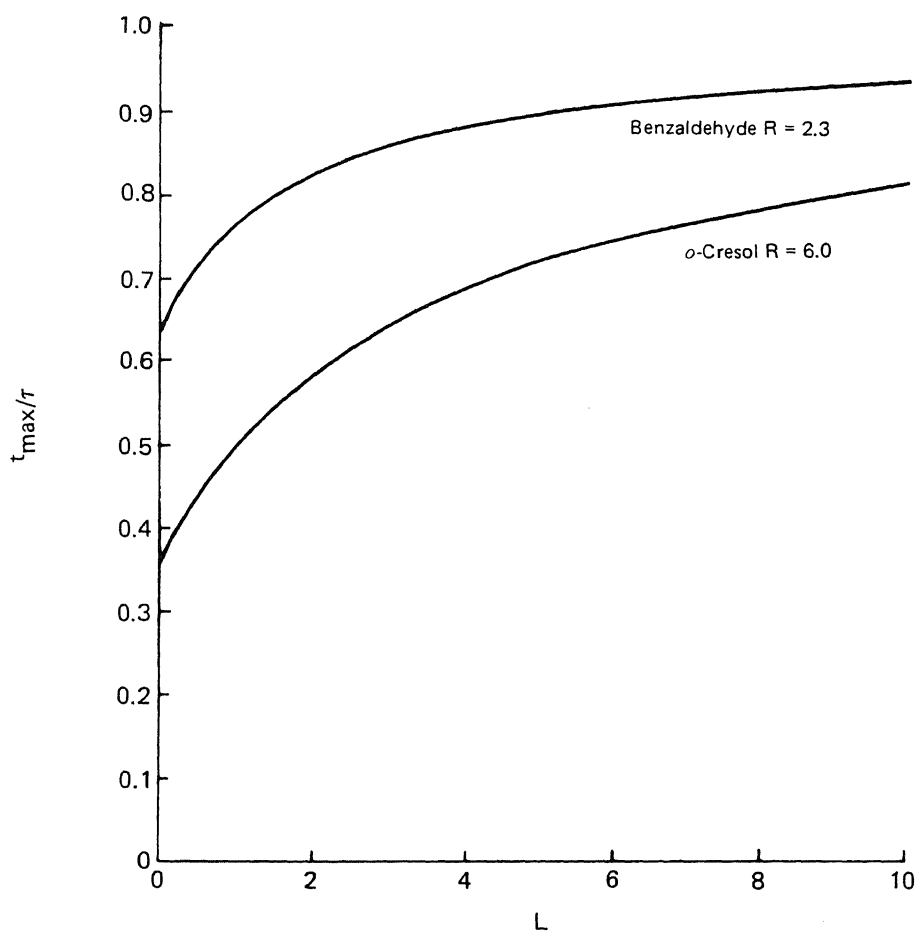


FIGURE 4-13. Fraction of toluene lifetime (Equation 34) for a product to reach maximum concentration as a function of dilution parameter L . This curve would be invalid for o-cresol if ozone is present.

reactant or product reacts with ozone or nitrate radical, then the situation is much more complex kinetically. This would be the case for cresol, but these equations should provide a good description of expected behavior for benzaldehyde as well as for other products. Product accumulation will be greatest in stagnant air, when L may approach zero. Under these conditions, benzaldehyde would reach a maximum concentration of approximately 1.8% of the initial toluene and *o*-cresol, which is more reactive, would reach 0.9% (Figure 4-12). Figure 4-12 shows that benzaldehyde would take approximately 65% of the *o*-cresol, 37% of the toluene lifetime to reach this maximum concentration. The expected toluene lifetime under these conditions (4-7) would be 50 daylight hours, or perhaps considerably less if stagnant air is photochemically reactive. The equations assume an air mass is isolated from sources during the course of reaction. The equations could be modified to take into account continuing emissions. The equations would then be site-specific.

The kinetics described above illustrate the types of mathematical relationships that are useful for predicting transport of alkyl benzenes and their primary photooxidation products. The goal in presenting these equations is more to provide an illustration than it is to do direct calculations. These equations are of course valid for many atmospheric gaseous species in addition to alkyl benzenes.

AQUATIC CONCENTRATIONS

Alkyl benzenes are recognized primarily as atmospheric contaminants, but a small percentage of the total amounts lost to the environment does enter aquatic and terrestrial systems. There is little information on the quantities that come from different sources. This has been discussed in Chapter 1.

It is generally known that most of the mass of low molecular weight hydrocarbons evaporates rapidly from a spill (National Academy of Sciences, 1975). Studies of actual and simulated oil spills in seawater indicate that virtually all hydrocarbons smaller than 1000 will be lost to the atmosphere within a few days (McAuliffe, 1976). Thus, it is probable that aquatic biota is exposed to relatively high concentrations of dissolved aromatics during the first few hours after an oil spill, but the concentrations and, presumably, the toxicity diminish as the oil "weathers," i.e., is affected by evaporation, dissolution, microbial metabolism, etc. (Mackay and Shiu, 1976).

Most alkyl benzenes used as solvents eventually evaporate from the atmosphere, but a relatively small proportion of them enter water. For example, approximately 0.7% (4,840 kg) of the toluene used as solvents is discharged annually in wastewater (U.S. Environmental Protection Agency, 1979).

Small, but undetermined amounts of alkyl benzenes are expected to enter water and soil from discarded products in landfills and in chemical waste dumps. Some of them enter the hydrosphere in runoff from agricultural and urban areas. Exhaust emissions from gasoline-powered boats are another small but direct source of aquatic alkyl benzenes (Weber et al., 1975). Mixed xylenes used in agriculture sprays are a potential source for both water and soil.

A number of U.S. drinking water supplies have been monitored for the presence of alkyl benzenes. Toluene was detected in 14 of 17 water supplies in concentrations ranging from trace to 1 $\mu\text{g/liter}$ (Coleman et al., 1976; Keith et al., 1976; Kleopfer, 1976; Kopfler et al., 1975; Suffet and Radziul, 1976). In a review of this subject, Suta (1979) reported that concentrations of toluene in one raw water sample and in three finished waters out of 11 surveyed ranged from 0.5 $\mu\text{g/liter}$ to 19 $\mu\text{g/liter}$. Alkyl benzenes have been detected in parts per billion levels in raw and finished drinking waters, river waters, and industrial effluents. A summary of these data is presented in Chapter 3.

Xylene isomers were detected but not quantified in five U.S. cities: Tuscaloosa, Alabama (Bertsch et al., 1975); Houston, Texas (Bertsch et al., 1975); Philadelphia, Pennsylvania (Suffet and Radziul, 1976); New Orleans, Louisiana (Dowty et al., 1975; Keith et al., (1976); and Washington, D.C. (Saunders et al., 1975). A concentration of 0.29 mg/liter xylene was found in the New Orleans drinking water; however, the concentration of individual isomers was not reported. Burnham et al. (1972) found 15 $\mu\text{g/liter}$ ethylbenzene in river water, chemical plant effluents, raw water, textile plant effluents, and well water. In a survey of contaminants in the drinking water of 10 U.S. cities, ethylbenzene was detected but not quantified in 6 of 10 samples (U.S. Environmental Protection Agency, 1975). This report indicated that alkylated benzenes were present in U.S. drinking water in concentrations of 10^{-6} g/liter.

Styrene has been detected in river waters in The Netherlands and West Virginia (Eurocop-Cost, 1976) and in effluents discharged from petroleum-refining (31 $\mu\text{g/liter}$), chemical (30 $\mu\text{g/liter}$), rubber (2.6-3 $\mu\text{g/liter}$), and textile manufacturing plants in the United States (Eurocop-Cost, 1976; Shackelford and Keith, 1976).

Recent studies of the coastal waters of the Gulf of Mexico have shown that aromatic hydrocarbons comprise 80% to 90% of the total dissolved volatile hydrocarbons (C_{14}) at most sampling sites. However, these hydrocarbons were only a few percent or less of the total dissolved hydrocarbons. Total concentrations of volatile aromatics (benzene, toluene, ethylbenzene, and xylenes) range from 20 ng/liter to 450 ng/liter (Sauer et al., 1978). Complete data for the alkyl benzenes are presented in Table 4-9. Sauer et al. (1978)

TABLE 4-9. Benzene and Its Alkyl Derivatives Contained in Surface Waters at Several Sites in the Gulf of Mexico

Aquatic Concentration (C), ng/liter^a, and Equilibrium Partial Pressure (P)

Benzene		Toluene		Ethylbenzene		m- and p-Xylene ^c		o-Xylene
C	P	C	P	C	P	C	P	C
15.8	1.1	4.5	.29	0.6	.068	10.2	1.02	2.1
32.5	2.3	376.0	24.5	4.5	.52	24.4	2.44	10.1
15.3	1.1	12.4	.81	1.8	.21	5.2	.52	2.0
101.0	7.1	34.7	2.3	0.8	.091	20.0	2.0	3.6
17.4	1.2	23.9	1.6	4.4	.50	21.0	2.1	6.0
9.3	0.65	5.9	.38	0.4	.046	2.7	.27	0.3
50.8	3.6	20.0	1.3	1.5	.17	9.9	.99	3.0
31.1	2.2	13.6	.89	1.1	.13	9.1	.91	2.3

^aFrom the data of Sauer et al., 1978.

^bCalculated using Henry's Law coefficients from Table 4-10.

^cAverage value taken for the Henry's Law coefficient.

developed a measurement technique far more sensitive than any used previously in order to detect these trace levels. They concluded from their results that hydrocarbons, especially the alkyl benzenes, are persistent in the marine environment.

Henry's law coefficients computed from the vapor pressure (Weast, 1971) and solubility data (Sutton and Calder, 1975) shown in Table 4-10 were used to calculate the gas phase concentrations of alkyl benzenes theoretically in equilibrium with the measurements of Sauer et al. (1978). The results (Table 4-9) are often consistent with concentrations expected over the Gulf of Mexico downwind from the Gulf Coast. Thus, the conclusion of Sauer et al. (1978) that the alkyl benzenes did not totally evaporate is not surprising. In fact, it is not at all certain whether the concentrations of alkyl benzenes measured in this study resulted from atmospheric transport from polluted regions or whether they were the direct result of ocean spills.

TRANSFER BETWEEN AIR AND WATER

Using the Henry's Law coefficients (H) as partition coefficients, it is possible to calculate the relative amounts of alkyl benzenes that would be present in a water column below an air column at equilibrium. If the heights of these two columns were the same, then the Henry's Law coefficient gives this ratio directly. This calculation neglects the decrease of pressure with altitude. For toluene, $H \equiv [\text{toluene}]_{\text{gas}} / [\text{toluene}]_{\text{liquid}} = 0.349$ for seawater. Thus, only 26% of the toluene would be present in the gas phase above the water if equilibrium were attained.

In shallow waters, or in deep waters where stratification occurs, it is likely that the atmospheric mixing layer is 10 to 100 times deeper than the aquatic mixing layer. In such water, 78% or 97%, respectively, of the toluene would exist in the gas phase. This estimate again neglects the decrease in atmospheric pressure with increased altitude.

Using a simple two-layer model (e.g., that of Liss and Slater, 1974), Mackay and Leinonen (1975) estimated that the aquatic lifetime of alkyl benzenes is represented by the ratio of the depth of the aquatic mixing layer to the transfer coefficient. For alkyl benzenes, Liss and Slater (1974) predicted that all resistance to transfer at the interface occurs in the liquid phase. They reported that the value of the transfer coefficient is 0.2 m/hr for the ocean. The lifetime would be approximately 5 hr at a 1-m depth, approximately 2 days at 10 m, and approximately 20 days at 100 m. Because this model assumes rapid turbulent mixing in the aquatic phase, it would underestimate the actual lifetimes. This model indicates that similar times would be required to reach equilibrium, regardless of whether the liquid or the gas phase was the source.

TABLE 4-10. Solubilities, Vapor Pressures, and Henry's Law Coeff
for Alkyl Benzenes at 25°C

Compound	Vapor pressure, atm ^a	Solubility in distilled water, mg/liter ^b	Henry's Law, distilled water ^c	Solubility in sea- water, mg/liter ^b
Toluene	.0352	534.8 \pm 4.9	.237	379.3 \pm 2.8
Ethylbenzene	.0128	161.2 \pm 0.9	.344	111.0 \pm 1.3
<u>o</u> -Xylene	.00862	170.5 \pm 2.5	.219	129.6 \pm 1.8
<u>m</u> -Xylene	.0106	146.0 \pm 1.6	.314	106.0 \pm 0.6
<u>p</u> -Xylene	.0113	156.0 \pm 1.6	.314	110.9 \pm 0.9
Isopropylbenzene	.00593	65.3 \pm 0.8	.446	42.5 \pm 0.2
1,2,4-Trimethylbenzene	.00299	59.0 \pm 0.8	.249	39.6 \pm 0.5
1,2,3-Trimethylbenzene	.00233	75.2 \pm 0.6	.152	48.6 \pm 0.5
1,3,5-Trimethylbenzene	.00371	48.2 \pm 0.3	.378	31.3 \pm 0.2
<u>n</u> -Butylbenzene	.00162	11.8 \pm 0.1	.753	7.09 \pm 0.07
<u>sec</u> -Butylbenzene	.00209	17.6 \pm 0.2	.651	11.9 \pm 0.2
<u>tert</u> -Butylbenzene	.00292	29.5 \pm 0.3	.543	21.2 \pm 0.3

^aWeast, 1971.

^bSutton and Calder, 1975.

^cCalculated as (vapor pressure, mol/liter)/(solubility, mol/liter).
To convert to (atm)/(mol/l) x RT, RT = 0.082 (gas constant) x 298°C.

Walsh et al. (1977) measured the rate at which xylene dissipated in irrigation canals where it had been applied for aquatic weed control. Applications of 740 mg/liter emulsified xylene had declined to less than 100 mg/liter by the time the canal water had traveled 16 km. The flow velocity of the water was not reported. The concentrations of xylene dissipated rapidly once the treated water reached cropland and were below detectable levels (0.2 mg/liter) in the return flows. Turbulence and mixing rates within the irrigation canals enhanced the rates of dissipation.

AQUATIC FATE

In the absence of aquatic removal processes, both freshwater and saltwater can be expected to contain alkyl benzenes in concentrations similar to those reported by Sauer et al. (1978), if such water is near anthropogenic sources of the compounds. Transport from land-based sources through the atmosphere should be sufficient to contaminate aquatic systems, even in the absence of aquatic spills.

If aquatic lifetimes are comparable to the above transfer times, then the Henry's Law solubilities will never be reached. Mill et al. (1980) have characterized the aquatic lifetime of cumene when it is oxidized by photochemically produced, dissolved hydroxyl and peroxy (RO_2) radicals. For this and similar compounds, the reaction rate with peroxy radicals was far greater than the rate with hydroxyl radicals. However, for all the mono-, di-, and trimethyl-substituted benzene derivatives, the estimated lifetimes are too long to be important, even for reactions with the peroxy radicals. In the presence of turbidity, these lifetimes would be even longer because of light attenuation and radical scavenging by particulate matter. Thus, it seems likely that biodegradation will be the primary fate of the alkyl benzenes in aquatic systems. This will be true regardless of whether the source was air, spills, or seepage. Microbial degradation is a complex process that varies with dissolved oxygen, water depth, presence of other critical nutrients, etc. (National Academy of Sciences, 1975). This topic is discussed further in Chapter 8.

The above estimates for the partitioning of alkyl benzenes between air and water may be applied directly to washout of these compounds by rain. Assuming as an upper limit that the rain is saturated with alkyl benzenes in the gas phase and that 1 cm of rain falls through 100 m of air, the ratio of concentrations can be obtained by the Henry's Law coefficients. On this basis it can be calculated that 0.04% toluene would be removed. Thus, washout should not be considered a significant removal process for these compounds.

FATE IN SOILS

There is very little information on the persistence or transport of alkyl benzenes in soil. These compounds are subject to degradation by soil microbes at variable rates that depend on soil types and other environmental factors. Toluene is probably degraded within a short time, whereas xylenes may persist for 6 months or longer. Small quantities of alkyl benzenes would be expected to volatilize from soils or be degraded rather quickly, but the fate of high concentrations in the soil is impossible to determine without more information (Miller et al., 1976).

SUMMARY

Alkyl benzenes are emitted into the atmosphere as air pollutants primarily from solvents and gasoline usage, and, to a lesser extent, from the use of diesel fuel. Other sources, most of which are industrial, contribute a far smaller amount on a national scale, but such sources may be significant locally. Urban levels of toluene normally range from 1 to 10 ppb but may be either 10 times lower or 5 times higher than these values. Because the higher molecular weight compounds are used in smaller amounts, they are found in lower concentrations in the environment.

Alkyl benzenes currently comprise between 25% and 40% of nonmethane hydrocarbons in urban and suburban atmospheres. Although total atmospheric hydrocarbons have declined significantly in some areas during the last 10 to 15 years, this trend may not continue. Furthermore, it is likely that alkyl benzenes will contribute a larger proportionate share of the total hydrocarbons in the future.

Minor amounts of alkyl benzenes are emitted into water from the exhausts of boats or ships, petroleum spills, seepage, or runoffs. Some of the emissions are attributed to the use of alkyl benzenes as herbicides. Predictions indicate that rapid equilibration between air and water should occur, and that the lifetime for shallow water should be on the order of hours. These predictions are borne out by the limited amount of data showing that most light hydrocarbons evaporate rapidly from the aquatic phase following their introduction by spills or from herbicides. The equilibrium between air and water is described by Henry's Law. Recent measurements of alkyl benzenes dissolved in surface waters of the Gulf of Mexico in the nanogram per liter concentration range are consistent with likely gas phase concentrations. In this case, the atmosphere may have been the source rather than spills or seepage.

Henry's Law indicates that water and air columns of equal height should contain roughly comparable amounts of all the alkyl benzenes

at saturation. However, because the atmospheric mixing layer is probably much deeper than the aquatic mixing layer, most of the alkyl benzenes should still be present in the atmosphere.

Rain does not appear to be a significant atmospheric removal process for any of the alkyl benzenes. Atmospheric concentrations of alkyl benzenes are reduced downwind from sources by dilution and chemical removal by hydroxyl radical.

The chemical lifetime of benzene and its alkyl derivatives is determined by the ambient concentration of hydroxyl radical. This concentration is variable, depending upon solar intensity, temperature, and other parameters. Their resultant average lifetimes range from 200 daylight hours for benzene, which is the least reactive aromatic, to 5 to 10 hr for the very reactive trimethylbenzenes.

Products of the atmospheric reaction of alkyl benzenes with hydroxyl radical have only been partially characterized. The fraction of the products that leave the gas phase to form aerosol or deposit on surfaces is high in simulation experiments carried out in containment vessels. The distribution of the products between gas and condensed phases in the open atmosphere is still not clear.

Alkyl benzenes have been shown to yield aldehydes, hydroxy-alkylbenzenes, and nitroalkylbenzenes as gas phase addition products. Low molecular weight oxidized ring fragments have been identified as well. Chief among these products is peroxyacetylnitrate (PAN), which is generated at high yield. Other gas phase products probably do not exceed a few percent of their parent hydrocarbon concentration at any time. Final oxidation products are carbon monoxide and carbon dioxide. The chief environmental effects of alkyl benzenes are probably their promotion of photochemical air pollution, an effect shared by other hydrocarbons as well. However, given the relatively high photochemical reactivity and the ambient concentrations of alkyl benzenes, they are undoubtedly of considerable environmental importance. But because the relevant processes involved in their atmospheric chemistry are not sufficiently understood, they are excluded from models currently used to control ozone. Thus, it is not yet possible to quantify their contribution relative to the contribution of other hydrocarbons.

REFERENCES

- Altshuller, A. P., and I. R. Cohen. 1963. Structural effects on the rate of nitrogen dioxide formation in the photo-oxidation of organic compound-nitric oxide mixtures in air. *Int. J. Air Water Pollut.* 7:787-797.
- Altshuller, A. P., W. A. Lonneman, F. D. Sutterfield, and S. L. Kopczynski. 1971. Hydrocarbon composition of the atmosphere of the Los Angeles Basin--1967. *Environ. Sci. Technol.* 5: 1009-1016.
- Altwick, E. R., R. A. Whitby, and W. N. Stasiuk. 1977. Ambient hydrocarbon levels at two elevated and some street level sites. Pp. 520-523 in S. Kasuga, N. Suzuki, T. Yamada, G. Kimura, K. Inagaki, and K. Onoe, eds. *Proceedings of the 4th International Clean Air Congress, Tokyo, May 16-20, 1977.* Japanese Union of Air Pollution Prevention Associations, Tokyo. [*Chemosphere* Abs. 88:141039q, 1978.]
- Atkinson, R., K. R. Darnall, and J. N. Pitts, Jr. 1978. Rate constraints for reaction of OH radicals and ozone with cresols at 300 \pm 1 K. *J. Phys. Chem.* 82:2759-2761.
- Atkinson, R., K. R. Darnall, A. C. Lloyd, A. M. Winer, and J. N. Pitts, Jr. 1979. Kinetics and mechanisms of the reactions of the hydroxyl radical with organic compounds in the gas phase. *Adv. Photochem.* 11:375-488.
- Bertsch, W., E. Anderson, and G. Holzer. 1975. Trace analysis of organic volatiles in water by gas chromatography-mass spectrometry with glass capillary columns. *J. Chromatogr.* 112:701-718.
- Burnham, A. K., G. V. Calder, J. S. Fritz, G. A. Junk, H. J. Svehla, and R. Willis. 1972. Identification and estimation of neutral organic contaminants in potable water. *Anal. Chem.* 44:139-144.
- Calvert, J. G. 1976. Hydrocarbon involvement in photochemical smog formation in Los Angeles atmosphere. *Environ. Sci. Technol.* 10:256-262.
- Calvert, J. G., and J. N. Pitts, Jr. 1966. *Photochemistry.* John Wiley & Sons, New York. 899 pp.
- Campbell, M. J., J. C. Sheppard, and B. F. Au. 1979. Measurement of hydroxyl concentration in boundary layer air by monitoring CO oxidation. *Geophys. Res. Lett.* 6:175-178.

- Chang, T. Y., J. M. Norbeck, and B. Weinstock. 1979. An estimate of the NO_x removal rate in an urban atmosphere. *Environ. Sci. Technol.* 13:1534-1537.
- Coleman, W. E., R. D. Lingg, R. G. Melton, and F. C. Kopfler. 1976. The occurrence of volatile organics in five drinking water supplies using gas chromatography/mass spectrometry. Pp. 305-327 in L. H. Keith, ed. *Identification and Analysis of Organic Pollutants in Water*. Ann Arbor Science Publishers, Inc., Ann Arbor, Mich.
- Crutzen, P. J., and J. Fishman. 1977. Average concentration of OH in the troposphere, and the budgets of CH_4 , CO, H_2 and CH_3CCl_3 . *Geophys. Res. Lett.* 4:321-324.
- Darnall, K. R., R. Atkinson, J. N. Pitts, Jr. 1979. Observation of biacetyl from the reaction of OH radicals with o-xylene. Evidence for ring cleavage. *J. Phys. Chem.* 83:1943-1946.
- Davis, D. D., W. Heaps, D. Philen, and T. McGee. 1979. Boundary layer measurements of the OH radical in the vicinity of an isolated power plant plume: SO_2 and NO_2 chemical conversion times. *Atmos. Environ.* 13:1197-1203.
- Demerjian, K. L., J. A. Kerr, and J. G. Calvert. 1974. The mechanism of photochemical smog formation. Pp. 1-262 in J. N. Pitts, Jr., and R. L. Metcalf, eds. *Advances in Environmental Science and Technology*, Volume 4. John Wiley & Sons, New York.
- Dimitriadis, B., and T. C. Wesson. 1972. Reactivity of exhaust aldehydes. *J. Air Pollut. Control Assoc.* 22:33-38.
- Dowty, B. J., D. R. Carlisle, and J. L. Laseter. 1975. New Orleans drinking water sources tested by gas chromatography-mass spectrometry: Occurrence and origin of aromatics and halogenated aliphatic hydrocarbons. *Environ. Sci. Technol.* 9:762-765.
- Eurocop-Cost. 1976. P. 101 in *A Comprehensive List of Polluting Substances Which Have Been Identified in Various Fresh Waters, Effluent Discharges, Aquatic Animals and Plants, and Bottom Sediments*. 2nd edition, EUCO/MDU/73/76, XII/476/76. Commission of the European Communities, Luxembourg.
- Gay, B. W., Jr., and J. J. Bufalini. 1971. Nitric acid and the nitrogen balance of irradiated hydrocarbons in the presence of oxides of nitrogen. *Environ. Sci. Technol.* 5:422-425.

- Glasson, W. A., and C. S. Tuesday. 1970. Hydrocarbon reactivities in the atmospheric photooxidation of nitric oxide. *Environ. Sci. Technol.* 4:916-924.
- Groblicki, P. J., and G. J. Nebel. 1971. The photochemical reaction of aerosols in urban atmospheres. Pp. 241-263 in C. S. Tuesday, ed. *Chemical Reactions in Urban Atmospheres: Proceedings of the Symposium held at General Motors Research Laboratories, Warren, Michigan, 1969.* American Elsevier, New York.
- Grosjean, D., and S. K. Friedlander. 1980. Formation of organic aerosols from cyclic olefins and diolefins. *Advances in Environ. Sci. Technol.* 10:435-473.
- Grovenstein, E., Jr., and A. J. Mosher. 1970. Reaction of atomic oxygen with aromatic hydrocarbons. *J. Am. Chem. Soc.* 92:3810-3812.
- Hendry, D. G. 1979. Reactions of aromatic hydrocarbons in the atmosphere. Pp. 85-91 in J. T. Herron, R. E. Huie, and J. A. Hodgeson, eds. *Chemical Kinetic Data Needs for Modeling the Lower Troposphere: Proceedings of a Workshop held at Reston, Virginia, May 15-17, 1978.* NBS Special Publication 557. U.S. Department of Commerce, National Bureau of Standards, Washington, D.C.
- Herron, J. T., R. E. Huie, and J. A. Hodgeson, eds. 1979. *Chemical Kinetic Data Needs for Modeling the Lower Troposphere: Proceedings of a Workshop held at Reston, Virginia, May 15-17, 1978.* NBS Special Publication 557. U.S. Department of Commerce, National Bureau of Standards, Washington, D.C.
- Heuss, J. M., and W. A. Glasson. 1968. Hydrocarbon reactivity and eye irritation. *Environ. Sci. Technol.* 2:1109-1116.
- Hoshino, M., H. Akimoto, and M. Okuda. 1978. Photochemical reactions of benzene, toluene, and ethylbenzene initiated by hydroxyl radicals in the gas phase. *Bull. Chem. Soc. Japan* 51:711-716. [Chem. Abs. 88:169346v, 1978.]
- Keith, L. H., A. W. Garrison, F. R. Allen, M. H. Carter, T. I. Floyd, J. D. Pope, and A. D. Thruston, Jr. 1976. Identification of organic compounds in drinking water from thirteen U.S. cities. Pp. 329-373 in L. H. Keith, ed. *Identification and Analysis of Organic Pollutants in Water.* Ann Arbor Science Publishers, Inc., Ann Arbor, Mich.

- Kenley, R. A., J. E. Davenport, and D. G. Hendry. 1978. Hydroxyl radical reactions in the gas phase. Products and pathways for the reaction of OH with toluene. *J. Phys. Chem.* 82: 1095-1096.
- Kleopfer, R. D. 1976. Analysis of drinking water for organic compounds. Pp. 399-416 in L. H. Keith, ed. *Identification and Analysis of Organic Pollutants in Water*. Ann Arbor Science Publishers, Inc., Ann Arbor, Mich.
- Kocmond, W. C., D. B. Kittelson, J. Y. Yang, and K. L. Demerjian. 1975. Study of aerosol formation in photochemical air pollution. Report No. EPA/650/3-75/007. U.S. Environmental Protection Agency, Washington, D.C. 191 pp.
- Kopczynski, S. L. 1964. Photo-oxidation of alkylbenzene-nitrogen dioxide mixtures in air. *Int. J. Air Water Pollut.* 8:107-120.
- Kopczynski, S. L., W. A. Lonneman, F. D. Sutterfield, and P. E. Darley. 1972. Photochemistry of atmospheric samples in Los Angeles. *Environ. Sci. Technol.* 6:342-347.
- Kopczynski, S. L., R. L. Kuntz, and J. J. Bufalini. 1975. Reactivities of complex hydrocarbon mixtures. *Environ. Sci. Technol.* 9:648-653.
- Kopfler, F. C., R. G. Melton, J. L. Mullaney, and R. G. Tardiff. 1975. Human exposure to water pollutants. Paper presented at Natl. Meet., Div. Environ. Chem., Am. Chem. Soc. 15(1): 185-187.
- Leighton, P. A. 1961. *The Photochemistry of Air Pollution*. Academic Press, New York. 300 pp.
- Leonard, M. J., E. L. Fisher, M. F. Brunelle, and J. E. Dickinson. 1976. Effects of the motor vehicle control program on hydrocarbons in the central Los Angeles atmosphere. *J. Air Pollut. Control Assoc.* 26:359-363.
- Liss, P. S., and P. G. Slater. 1974. Flux of gases across the air-sea interface. *Nature* 247:181-184.
- Lonneman, W. A., T. A. Bellar, and A. P. Altshuller. 1968. Aromatic hydrocarbons in the atmosphere of the Los Angeles Basin. *Environ. Sci. Technol.* 2:1017-1020.
- Mackay, D., and P. J. Leinonen. 1975. Rate of evaporation of low-solubility contaminants from water bodies to atmosphere. *Environ. Sci. Technol.* 9:1178-1180.

- Mackay, D., and W. Y. Shiu. 1976. Aqueous solubilities of weathered northern crude oils. *Bull. Environ. Contam. Toxicol.* 15:101-109.
- McAuliffe, C. D. 1977. Evaporation and solution of C₂ to C₁₀ hydrocarbons from crude oils on the sea surface. Pp. 363-372 in D. A. Wolfe, ed. *Fate and Effects of Petroleum Hydrocarbons in Marine Organisms and Ecosystems*. Pergamon Press, New York.
- Mill, T., D. G. Hendry, and H. Richardson. 1980. Free-radical oxidants in natural waters. *Science* 207:886-887.
- Miller, T. A., D. H. Rosenblatt, J. C. Dacre, J. G. Pearson, and R. K. Kulkarni. 1976. Problem Definition Studies on Potential Environmental Pollutants. IV. Physical, Chemical, Toxicological, and Biological Properties of Benzene; Toluene; Xylenes; and Para-Chlorophenyl Methyl Sulfide, Sulfoxide, and Sulfone. (Available from the National Technical Information Service, Springfield, Va., as AD/A-040 435.) Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Md. 95 pp.
- National Academy of Sciences. 1975. Petroleum in the Marine Environment. Workshop in Inputs, Fates, and the Effects of Petroleum in the Marine Environment, May 21-25, 1973, Airlie, Virginia. National Academy of Sciences, Washington, D.C. 107 pp.
- National Academy of Sciences. 1976. Vapor-Phase Organic Pollutants. Volatile Hydrocarbons and Oxidation Products. National Academy of Sciences, Washington, D.C. xiii + 411 pp.
- National Academy of Sciences. 1977. Ozone and Other Photochemical Oxidants. National Academy of Sciences, Washington, D.C. 719 pp.
- Niki, H., P. D. Maker, C. M. Savage, and L. P. Breitenbach. 1978. Relative rate constants for the reaction of hydroxyl radical with aldehydes. *J. Phys. Chem.* 82:132-134.
- O'Brien, R. J. 1974. Photostationary state in photochemical smog studies. *Environ. Sci. Technol.* 8:579-583.
- O'Brien, R. J., J. R. Holmes, and A. H. Bockian. 1975a. Formation of photochemical aerosol from hydrocarbons: Chemical reactivity and products. *Environ. Sci. Technol.* 9:568-576.
- O'Brien, R. J., J. W. Vanderzanden, and R. R. Easton. 1975b. Fate of toluene in polluted atmospheres. American Chemical Society, Pacific Conference on Chemistry and Spectroscopy, North Hollywood California, October 28-30, 1975 (Abstract 74, p. 50).

- O'Brien, R. J., P. J. Green, and R. M. Doty. 1979a. [Comment on reactions of aromatic compounds in the atmosphere by D. G. Hendry.] Pp. 93-95 in J. T. Herron, R. E. Huie, and J. A. Hodgeson, eds. 1979. Chemical Kinetic Data Needs for Modeling the Lower Troposphere: Proceedings of a Workshop held at Reston, Virginia, May 15-17, 1978. NBS Special Publication 557. U.S. Department of Commerce, National Bureau of Standards, Washington, D.C.
- O'Brien, R. J., P. J. Green, and R. A. Doty. 1979b. [Comment on tropospheric chemistry of nitrogen oxides--a summary of the status of chemical kinetic data by R. A. Cox.] Pp. 74-77 in J. T. Herron, R. E. Huie, and J. A. Hodgeson, eds. Chemical Kinetic Data Needs for Modelling the Lower Troposphere: Proceedings of a Workshop held at Reston, Virginia, May 15-17, 1978. NBS Special Publication 557. U.S. Department of Commerce, National Bureau of Standards, Washington, D.C.
- O'Brien, R. J., P. J. Green, and R. A. Doty. 1979c. Progress Report for the U.S. Environmental Protection Agency, Grant R804764-03, Reactions of Aromatic Hydrocarbons of Chemistry, Portland State University, Portland, Oregon.
- O'Brien, R. J., P. J. Green, and R. A. Doty. 1979d. Rate constant for the reaction $\text{NO}_2 + \text{OH} + \text{M} \rightarrow \text{HNO}_3$ measured under simulated atmospheric conditions using a novel analysis procedure. J. Phys. Chem. 83:3302-3305.
- O'Brien, R. J., P. J. Green, R. A. Doty, J. W. Vanderzander, R. R. Easton, and R. P. Irwin. 1979e. Interaction of oxides of nitrogen and aromatic hydrocarbons under simulated atmospheric conditions. Chapter 11, pp. 189-220 in D. Grosjean, ed. Nitrogenous Air Pollutants; Chemical and Biological Implications. Ann Arbor Science Publishers, Inc., Ann Arbor, Mich.
- Pellizzari, E. D. 1979. Information on the Characterization of Ambient Organic Vapors in Areas of High Chemical Pollution. Control No. 68-02-2721, Health Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, N.C. 134 pp.
- Perner, D., D. H. Ehhalt, H. W. Pätz, U. Platt, E. P. Röth, and A. Volz. 1976. OH-radicals in the lower troposphere. Geophys. Res. Lett. 3:466-468.
- Perry, R. A., R. Atkinson, and J. N. Pitts, Jr. 1977. Kinetics and mechanism of the gas phase reaction of OH radicals with aromatic hydrocarbons over the temperature range 296-473 K. J. Phys. Chem. 81:296-304.

- Pilar, S., and W. F. Graydon. 1973. Benzene and toluene distribution in the Toronto atmosphere. Environ. Sci. Technol. 7:628-631.
- Ripperton, L. A., J. E. Jeffries, and O. White. 1972. Formation of aerosols by reaction of ozone with selected hydrocarbons. Pp. 219-231 in R. F. Gould, ed. Photochemical Smog and Ozone Reactions. Two Symposia Sponsored by Divisions of the American Chemical Society at the 161st ACS Meeting at Los Angeles, California, March 29, 1971 and April 1, 1971. Advances in Chemistry Series 113. American Chemical Society, Washington, D.C.
- Robinson, E., R. A. Rasmussen, H. H. Westberg, and M. W. Holdren. 1973. Nonurban, nonmethane low molecular weight hydrocarbon concentrations related to air mass identification. J. Geophys. Res. 78:5345-5351.
- Russell, P. A. 1977. Denver Air Pollution Study--1973. Proceedings of a Symposium. Volume II, Final Report, January 1974-June 1974. Report No. EPA/600/9-77/001. (Available from National Technical Information Service, Springfield, Va., as PB-264 216/3BE.) Atmospheric Chemistry and Physics Division, Denver Research Laboratory, Colorado Environmental Sciences Research Laboratory, Research Triangle Park, N.C. 183 pp.
- Sauer, T. C., Jr., W. M. Sackett, and L. M. Jeffrey. 1978. Volatile liquid hydrocarbons in the surface waters of the Gulf of Mexico. Marine Chemistry 7:1-16.
- Saunders, R. A., C. H. Blachly, T. A. Kovacina, R. A. Lamontagne, J. W. Swinnerton, and F. E. Saalfeld. 1975. Identification of volatile organic contaminants in Washington, D.C. municipal water. Water Res. 9:1143-1145.
- Schwartz, W., P. W. Jones, C. J. Riggle, and D. F. Miller. 1977. Chemical Characterization of Model Aerosols. Report No. EPA-650/3-74-011. (Available from the National Technical Information Service, Springfield, Va., as PB-238 557.) Battelle Columbus Laboratories, Columbus, Ohio.
- Sexton, K., and H. Westberg. 1980. Ambient hydrocarbon and ozone measurements downwind of a large automotive painting plant. Environ. Sci. Technol. 14:329-332.
- Shackelford, W. M., and L. H. Keith. 1976. Pp. 213-214 in Frequency of Organic Compounds Identified in Water. Report No. EPA-600/4-76-062. U.S. Environmental Protection Agency, Office of Research and Development, Environmental Research Laboratory, Athens, Ga.

- Singh, H. B. 1977. Atmospheric halocarbons: Evidence in favor of reduced average hydroxyl radical concentration in the troposphere. *Geophys. Res. Lett.* 4:101-104.
- Singh, H. B., F. L. Ludvig, and W. B. Johnson. 1978. Tropospheric ozone: Concentrations and variabilities in clean remote atmospheres. *Atmos. Environ.* 12:2185-2196.
- Singh, H. B., L. J. Salas, A. Smith, and H. Shigeishi. 1979. Atmospheric Measurements of Selected Toxic Organic Chemicals. Interim Report. Report prepared for the U.S. Environmental Protection Agency, Research Triangle Park, N.C., by Stanford Research Institute International, Menlo Park, Calif.
- Spicer, C. W., and P. W. Jones. 1977. The fate of aromatic hydrocarbons in photochemical smog systems: Toluene. *J. Air Pollut. Control Assoc.* 27:1122-1125.
- Stephens, E. R. 1969. The formation, reactions, and properties of peroxyacylnitrates (PANs) in photochemical air pollution. Pp. 119-146 in J. N. Pitts, Jr., and R. L. Metcalf, eds. *Advances in Environmental Sciences, Volume 1.* Wiley-Interscience, New York.
- Stephens, E. R. 1973. Hydrocarbons in Polluted Air: Summary Report. Coordinating Research Council Report CRC-APRAC-CAPA-5-68-1. (Available from the National Technical Information Service, Springfield, Va., as PB-230 993.) Statewide Air Pollution Research Center, University of California, Riverside. 86 pp.
- Suffet, I. H., and J. V. Radziul. 1976. Analysis of organic pollutants in drinking water. International Conference on Environmental Sensing and Assessment, September 14-19, Las Vegas, Nevada, Volume 2, Paper 30-1. Institute of Electronic and Electrical Engineers, Inc., New York.
- Suta, B. E. 1979. Nonoccupational Exposures to Alkylbenzenes from Their Use as Solvents. Stanford Research Institute International, Menlo Park, Calif. [57] pp.
- Sutton, C., and J. A. Calder. 1975. Solubility of alkylbenzenes in distilled water and seawater at 25.0°C. *J. Chem. Eng. Data* 20:320-322.
- Tannahill, G. K. 1976. The hydrocarbon/ozone relationship in Texas. Pp. 26-37 in Specialty Conference on Ozone/Oxidants--Interactions with the Total Environment. Air Pollution Control Association, Pittsburgh, Pa.

- U.S. Environmental Protection Agency. 1975. Preliminary Assessment of Suspected Carcinogens in Drinking Water: Report to Congress. Report No. EPA-560/4-75-005. (Available from the National Technical Information Service, Springfield, Va., as PB-250 961.) U.S. Environmental Protection Agency, Washington D.C. 107 pp.
- U.S. Environmental Protection Agency. 1978. Air Quality Criteria for Ozone and Other Photochemical Oxidants. Report No. EPA-600/8-78-004. Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C.
- U.S. Environmental Protection Agency. 1979. Toluene. Ambient Water Quality Criteria. Criteria and Standards Division, Office of Water Planning and Standards, U.S. Environmental Protection Agency, Washington, D.C.
- Walsh, D. F., J. G. Armstrong, T. R. Bartley, H. A. Salman, and P. A. Frank. 1977. Residues of Emulsified Xylene in Aquatic Weed Control and Their Impact on Rainbow Trout. Report No. REC-ERC-76-11. (Available from the National Technical Information Service, Springfield, Va., as PB-267 270.) Bureau of Reclamation, Engineering and Research Center, Denver, Co. 24 pp.
- Wang, C. C., L. I. Davis, Jr., C. H. Wu, S. Japar, H. Niki, and B. Weinstock. 1975. Hydroxyl radical concentrations measured in ambient air. Science 189:797-800.
- Weast, R. C., ed. 1971. Handbook of Chemistry and Physics, 52nd edition, Section D. Chemical Rubber Co., Cleveland, Ohio. 238 pp.
- Weber, W. J., Jr., D. E. Cole, and J. C. Posner. 1975. Analysis of Emissions from Outboard Two Cycle Marine Engines. Final Report. Report No. EPA/670/2-75-061. (Available from the National Technical Information Service, Springfield, Va., as PB-242 174.) Boating Industry Associations, Chicago, Ill. 266 pp.

CHAPTER 5

METABOLISM OF ALKYL BENZENES

There have been considerably more studies on the metabolism of alkyl benzenes in mammals than in nonmammalian species. Moreover, the various steps involved in the conversion of alkyl benzenes to their end products in mammals are fairly well understood.

Although metabolic studies in all organisms are of considerable importance to the evaluation of the disposition of alkyl benzenes in the environment, few such investigations have been performed in nonmammalian species. The degradation of alkyl benzenes by various microbial species has received the most attention, whereas little information is available on the metabolism of alkyl benzenes in insect species and higher plants. The literature contains no information on the metabolism of these compounds in birds, fish, or other major groups of organisms.

METABOLISM IN MAMMALS

In mammals, enzymes convert alkyl benzenes to many different metabolites (Williams, 1959). The formation rates of these metabolites may differ markedly among animal species and among certain strains and individuals within a species. Moreover, the activity of the enzymes may be altered considerably by compounds that are present in the environment. Such alterations contribute to the metabolic variability of these compounds.

The initial step in the metabolism of alkyl benzenes is hydroxylation, which is catalyzed by cytochrome P-450 enzymes (Daly, 1971). This process occurs mainly in the endoplasmic reticulum of the liver and, probably, to a lesser extent in the kidney, intestine, lung, and skin. Hydroxylation may take place either on the aromatic ring or on the alkyl group, but the conversion of the alkyl group to alcohols usually predominates. A metabolite that is a primary alcohol is usually oxidized first to an aldehyde by alcohol dehydrogenase and then to a carboxylic acid by aldehyde dehydrogenase and aldehyde oxidase (McMahon, 1971). Long-chain carboxylic acids then undergo β -oxidation by mitochondrial enzymes until either benzoic acid or phenylacetic acid is formed (Williams, 1959). In most mammalian species these acids are conjugated with glycine to form hippuric acid and phenaceturic acid. However, in Anthropoidae, including human beings, phenylacetic acid is also conjugated with glutamine to form phenacetylglutamine (James et al., 1972). In some instances,

the primary metabolite is a secondary alcohol, which may be converted to a ketone. But frequently, the ketone may be reduced back to the alcohol by reduced nicotinamide adenine dinucleotide phosphate (NADPH)- or reduced nicotinamide adenine dinucleotide (NADH)-dependent reductases, thereby establishing cyclic oxidation and reduction (McMahon, 1971). Secondary and tertiary alcohols often become conjugated to form glucuronides.

Alkenes are usually oxidized by cytochrome P-450 enzymes to epoxides, which react with nucleophiles, such as glutathione in the liver or with water, both enzymatically and nonenzymatically, to form glycols. The glycols in turn may become oxidized to hydroxy ketones, hydroxy acids, or α -keto acids, or they may be converted to glucuronides.

In addition to oxidation of the side chains of alkyl benzenes, the aromatic ring may become oxidized by cytochrome P-450 enzymes to arene oxides, which are subsequently rearranged to phenols (Daly, 1971). Arene oxides of halobenzenes and polycyclic hydrocarbons frequently react with nucleophiles such as glutathione and are hydrolyzed to dihydrodiols by epoxide hydratase, but it is not known if the arene oxides of the alkyl benzenes undergo these reactions. The phenols may be conjugated to form glucuronides or ether sulfates. Conceivably, the phenols could also undergo further epoxidation to form other chemically reactive metabolites that either react with nucleophilic compounds or are rearranged to hydroquinone derivatives. But such reactions have not been demonstrated with the phenolic derivatives of the alkyl benzenes.

Toluene

Absorption. In mammals, toluene may be absorbed via inhalation, ingestion, or absorption through the skin. Åstrand *et al.* (1972) reported that the average concentration of toluene in arterial blood reached a relatively constant value within 20 to 30 minutes after volunteers were exposed to 100 ppm or 200 ppm of toluene vapor. Blood concentrations were 1 $\mu\text{g/ml}$ and 2 $\mu\text{g/ml}$, respectively. Other studies have shown that the blood-to-gas partition coefficient ranges from approximately 12.4 to 15.6 (Lindqvist, 1977; Sato *et al.*, 1974; Sherwood, 1976). The time required to reach these relatively constant values could be shortened if pulmonary ventilation is increased through exercise.

Orally administered toluene is absorbed less rapidly. In rats, the maximum blood concentration was not observed until 2 to 3 hr after oral administration, whereas the maximum was reached within 15 to 30 minutes during inhalation exposures (Pyykko *et al.*, 1977). Dutkiewicz and Tyras (1968a, b) reported that toluene is absorbed

through the skin slowly. In humans, approximately 14 to 23 mg/cm²/hr was absorbed when the skin was exposed to pure liquid toluene. These investigators calculated that exposure of both hands to toluene for 1.5 minutes would be equivalent to inhalation exposure of humans to an atmosphere containing 26.6 ppm for 8 hr.

Disposition. After it is absorbed, toluene is rapidly distributed to the highly vascular tissues, including the brain, and eventually accumulates in adipose tissues. Consequently, obese people tend to accumulate more toluene than do lean people (Carlsson and Lindqvist, 1977). Approximately 15% to 20% of a dose of toluene is eliminated unchanged by the lungs of humans (Nomiya and Nomiya, 1974) and rabbits (Smith et al., 1954). Almost all of the rest of the dose is excreted as hippuric acid (El Masry et al., 1956; Smith et al., 1954). In rats, approximately 0.5% to 1.1% of the dose is converted to o-cresol and p-cresol and is excreted as glucuronide and sulfate conjugates (Bakke and Scheline, 1970) (see Figure 5-1).

The elimination of toluene from mammals may be represented by a three-compartment model. For example, Bergman (1979) has fitted the exhalation rate of unchanged toluene from mice to the following equation:

$$\% \text{ dose/min} = 0.294 e^{-0.0659t} + 0.111 e^{-0.0236t} + 0.0057 e^{-0.0044t}$$

where % dose/min is the excretion rate (percentage of dose exhaled per minute), e is exponential function, and t is time in minutes.

Integration of the equation provides an estimate of the percent of the dose that is excreted unchanged:

$$AUC_{\text{rate}} = 4.46 + 4.70 + 1.30 = 10.46$$

where AUC is the area under the curve.

Thus, the half-life of the terminal phase is approximately 2.5 hr, which suggests that the mice would have to be exposed to toluene for longer than 10 hr before the levels of toluene in the blood would reach a steady state. However, the relative areas under the curve of the three phases indicate that a considerable proportion of the steady-state concentration will be achieved during the first half hour. As indicated by the equation, more than 95% of the toluene is eliminated from the body within the first 8 hr.

The short half-life of the terminal phase indicates that the elimination of toluene from adipose tissue is not unusually slow (Pyykko et al., 1977). Unfortunately, no one appears to have calculated the

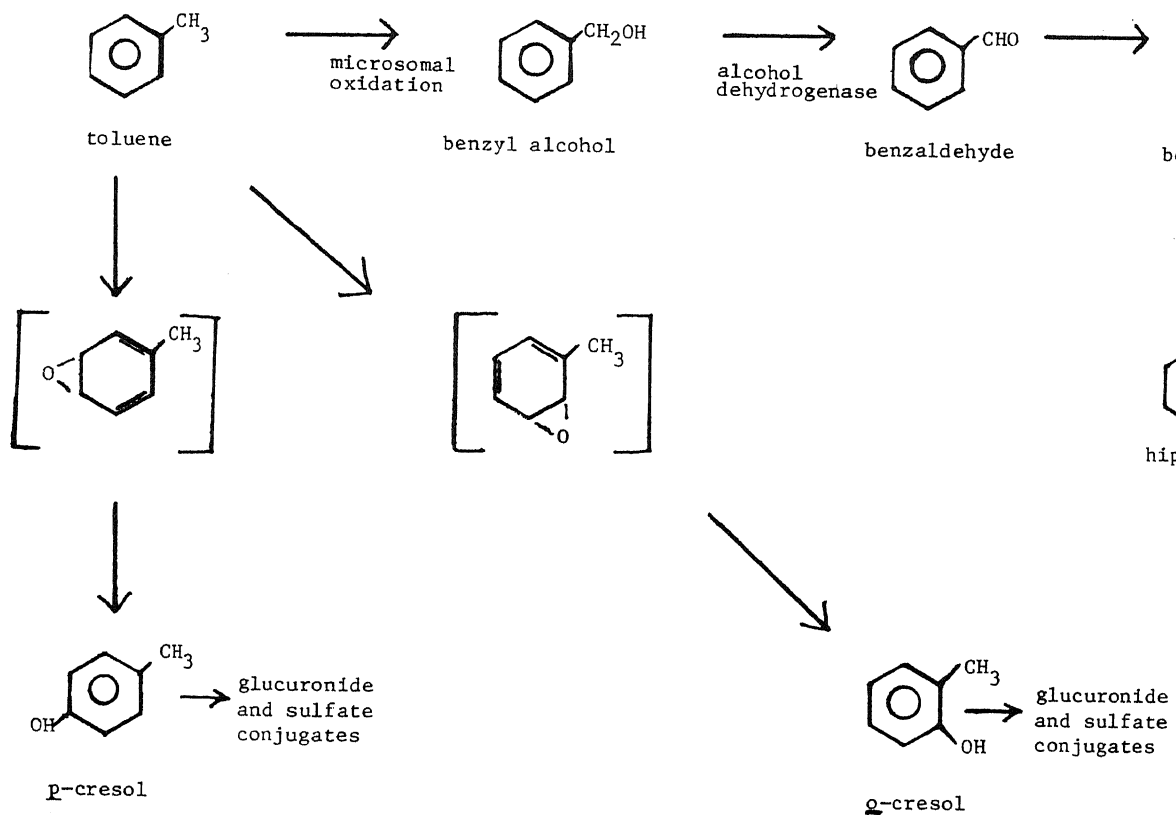


FIGURE 5-1. Metabolic pathways for toluene.

total body clearance of toluene. Because of the limitations of the available data, it is not possible to estimate the presystemic clearance of toluene by the liver or the availability of orally administered toluene.

The amount of hippuric acid excreted in the urine of humans who have been exposed to high concentrations of toluene is approximately proportional to the concentration of toluene in the atmosphere. However, the validity of urinary hippurate assays as indicators of the severity of occupational exposure to toluene is questionable. Benzoic acid and its precursors in foods cause levels of hippuric acid to be found in the urine of people not exposed to toluene (Gerarde, 1960). The finding of several groups of investigators (Arató-Sugár, 1968; Capellini and Alessio, 1971; Pagnotto and Lieberman, 1967; U.S. Department of Health, Education, and Welfare, 1973) that there are wide variations in the amount of hippuric acid excreted in the urine of different people may be due to the presence of hippuric acid precursors in their diet.

The mechanism of metabolism of toluene is probably similar to that of p-nitrotoluene (Gillette, 1959). If so, then toluene is converted initially to benzyl alcohol by cytochrome P-450 enzymes in the endoplasmic reticulum of the liver. In turn, the benzyl alcohol is oxidized to benzaldehyde by alcohol dehydrogenase and, subsequently, to benzoic acid by aldehyde dehydrogenase in the soluble fraction of liver homogenates. The benzoic acid is then activated by enzymes in liver mitochondria to form a coenzyme A derivative, which combines with glycine to form hippuric acid (Schachter and Taggart, 1953, 1954).

Prior exposure to compounds other than toluene may affect the rate at which toluene is converted to benzyl alcohol (Ikeda and Ohtsuji, 1971). For example, pretreatment of rats with phenobarbital, which increases cytochrome P-450 activity, decreases the concentration of toluene and increases the concentration of benzoic acid in blood. In accord with these findings, pretreatment of rats with phenobarbital increases the metabolism of p-nitrotoluene by liver microsomes. But the finding that the pretreatment does not change the rates at which p-nitrobenzyl alcohol is metabolized or p-nitrobenzoic acid is conjugated with glycine indicates that only the cytochrome P-450 enzyme is induced.

The formation of o-cresol and p-cresol is also catalyzed by cytochrome P-450 enzymes in liver microsomes (Daly, 1971). These metabolites are presumably synthesized through the formation of arene oxides followed by nonenzymatic rearrangements. In the formation of p-cresol, a part of the hydrogen in the para position migrates to the meta position.

It is not clear whether the toxic effects of toluene are mediated by its metabolites. It seems plausible that most of the toxicity is mediated by the parent compound since SKF 525-A [2-(4-aminophenyl)-2,2-diphenylvalerate hydrochloride] and carbon tetrachloride, which inhibit liver cytochrome P-450 enzymes, prolong toluene-induced narcosis and increase the lethality of toluene in rats (Koga and Ohmiya, 1978). Moreover, the arene oxides may rearrange to phenols too rapidly to produce toxic effects. There is no evidence for the formation of other metabolites such as dihydrodiols, catechols, or mercapturic acids, which are frequently formed from arene oxides. Koga and Ohmiya (1978) observed that pyrazole, which inhibits catalase, also enhances lethality and narcosis. This finding raises the possibility that the toluene-induced effects may be potentiated partly by the formation of benzyl alcohol. Nevertheless, pyrazole may still exert its potentiating effects on the toxicity of toluene by inhibiting the metabolism of the parent compound.

Xylene

Absorption. All of the xylene isomers enter the body rapidly via the inhalation route and less rapidly by absorption from the gastrointestinal tract (Gerarde, 1960) or through the skin (Dutkiewicz and Tyras, 1968b). The blood-to-gas partition ratio for xylene has been calculated to be between 29:1 (Åstrand, 1976) and 42:1 (Sherwood, 1976). The rate at which xylene is absorbed through human skin that is immersed in liquid xylene has been estimated to be between 4.5 and 9.6 mg/cm²/hr (Dutkiewicz and Tyras, 1968b).

Disposition. Like the other alkyl benzenes, xylene is distributed rapidly into all tissues of the body, especially into the bone marrow, brain, spleen, and adipose tissue (Fabre *et al.*, 1979). The pharmacokinetics of *m*-xylene in rats and mice fit a three-compartment model (Bergman, 1979). Changes in the rate at which xylene is exhaled by mice fit the following equation:

$$(\% \text{ dose/min})_{\text{m-xylene}} = 0.137 e^{-0.0990t} + 0.0021 e^{-0.0143t} + 0.0022 e^{-0.0001t}$$

Integration of the equation, AUC_{rate} , provides an estimate of the dose exhaled into the atmosphere:

$$AUC_{\text{rate}} = 1.38 + 1.47 + 0.96 = 3.81$$

The rather even distribution of the areas under the curve implies that the ratio of the rate constant for the metabolism of *m*-xylene to the rate constant for exhalation is approximately 1:1.

rate constants of distribution is rather large but not as large as the ratio for toluene. Unfortunately, neither the individual rate constants nor the total body clearance can be estimated directly from the available data. Therefore, it is not possible to calculate the significance of a first-pass effect. The approximately 5-hr half-life of the terminal phase indicates that exposure of the mice would have to exceed 20 hr for a true steady state to be reached. But the relative positions of the areas under the curve suggest that the concentration would have reached approximately 80% of the steady-state level within 6 hr. Thus, more than 90% of the dose should be eliminated from mice within 24 hr. Comparable studies in humans have not been conducted, but Sedivec and Flek (1976) reported that only 5% of a dose of a mixture of xylenes was exhaled. Their finding that 95% of the urinary metabolites was excreted within 10 hr indicates that the total body clearances of the xylenes are rather high.

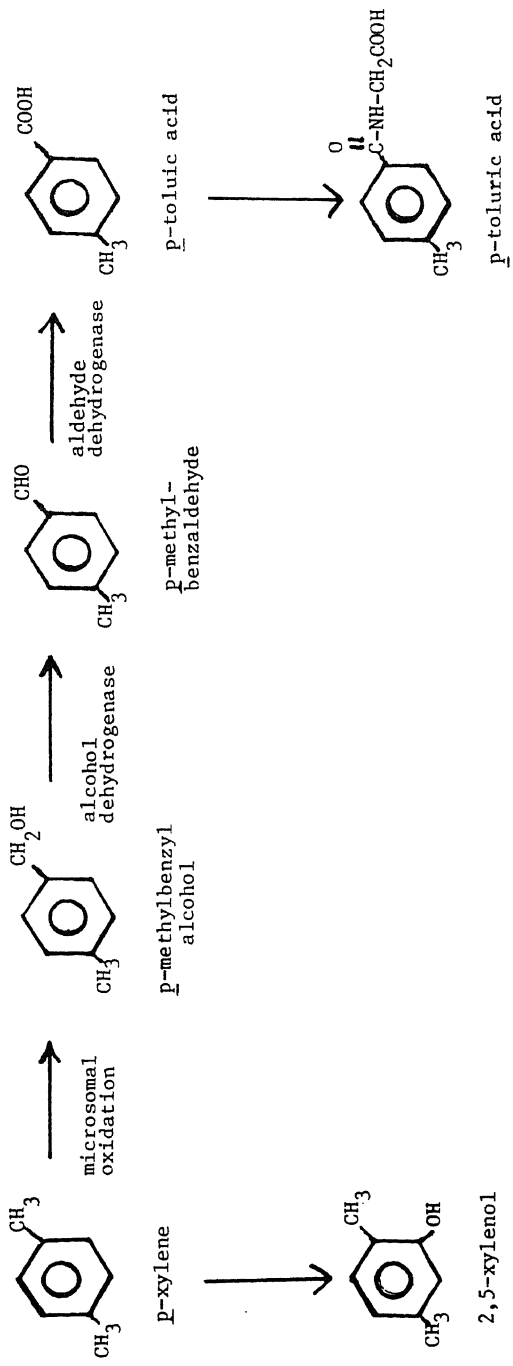
The xylenes undergo side-chain oxidation to methylbenzoic acids, which in turn are conjugated with glycine and excreted into urine as toluric acids in all mammals studied, including dogs, humans, rabbits, rats, and guinea pigs (Figure 5-2). In rabbits, for example, approximately 81% of a 1.7-g dose of m-xylene and 88% of a 1.7-g dose of p-xylene were oxidized to m- or p-toluic acids, respectively, and excreted mainly as their glycine conjugates (Bray et al., 1949). Also in rabbits, approximately 61% of a dose of o-xylene was converted to o-toluic acid; however, in contrast to the acids formed from the other isomers, most of the o-toluic acid was excreted in its unconjugated form.

In addition to side-chain oxidation, the xylenes undergo ring hydroxylation, but only to a minor extent (Bakke and Scheline, 1970). In rats, approximately 1% of a dose (100 mg/kg) of p-xylene was converted to 2,5-xyleneol, 0.9% of m-xylene was converted to 2,4-xyleneol, and 0.1% of o-xyleneol was converted to 3,4-xyleneol.

During the conversion of xylenes to toluic acids, the parent compounds are first converted to methylbenzyl alcohols by enzymes (presumably cytochrome P-450) in microsomes of the liver and lung (Harper, 1975; Harper et al., 1977). The alcohols are then oxidized to the toluic acids by enzymes in the soluble fraction of the liver (presumably alcohol and aldehyde dehydrogenases).

Pretreatment of rats with phenobarbital or 3-methylcholanthrene markedly increases the activity of the hepatic enzyme that converts p-xylene to p-methylbenzyl alcohol, but does not alter the enzyme in the lungs (Harper et al., 1977).

Patel et al. (1978, 1979) reported that the pretreatment of mice with individual xylene isomers did not alter the activity of



cytochrome P-450 in the liver. However, the administration of p-xylene to rabbits inactivated cytochrome P-450 in the lung.

Trimethylbenzenes

Little is known about the uptake and distribution in tissues of 1,2,3-trimethylbenzene, 1,2,4-trimethylbenzene (pseudocumene), or 1,3,5-trimethylbenzene (mesitylene) in mammals. Nevertheless, it may be assumed that these compounds would be absorbed rapidly and distributed to all body tissues in much the same way as the xylenes, which contain two methyl groups.

In dogs, pseudocumene is converted to o-xylic acid (3,4-dimethylbenzoic acid) (Jacobsen, 1879). Mesitylene is converted to mesitylenic acid (3,5-dimethylbenzoic acid), which is excreted by dogs and rabbits partly as the glycine conjugate (Filippi, 1914a, b; Nencki, 1873). (See Figure 5-3.)

Small amounts of mesitylene are converted to 2,4,6-trimethylphenol and p-hydroxymesitylenic acid (Curci, 1894).

Ethylbenzene

Absorption. Ethylbenzene may enter the body via the inhalation route or via absorption from the gastrointestinal tract or through the skin. Although the pharmacokinetics of the substance has not been studied extensively, there is no reason to believe that the rates of absorption and distribution into the various tissues of the body would differ markedly from those of toluene or styrene. The rate at which ethylbenzene is absorbed through the skin of human hands and forearms that have been immersed in the pure solvent ranges from 22 to 33 mg/cm²/hr (Dutkiewicz and Tyras, 1967). At these rates, the amount absorbed through both hands in 1 minute would be equivalent to the amount of ethylbenzene inhaled for 8 hr from an atmosphere containing 0.1 mg/liter.

Disposition. In rabbits receiving ethylbenzene, approximately 30% to 35% of the dose is converted to hippuric acid, approximately 30% to 35% is converted to methylphenylcarbonyl glucuronide, and approximately 10% to 20% is converted to phenaceturic acid (El Masry et al., 1956). Minor urinary metabolites, each of which constitutes less than 2% of the dose, are mandelic acid and o-, p-, and m-hydroxyacetophenone (Kiese and Lenk, 1974).

Figure 5-4 shows the metabolic pathways for ethylbenzene. Approximately 60% of an inhaled dose (Bardodej and Bardodejova, 1970) and

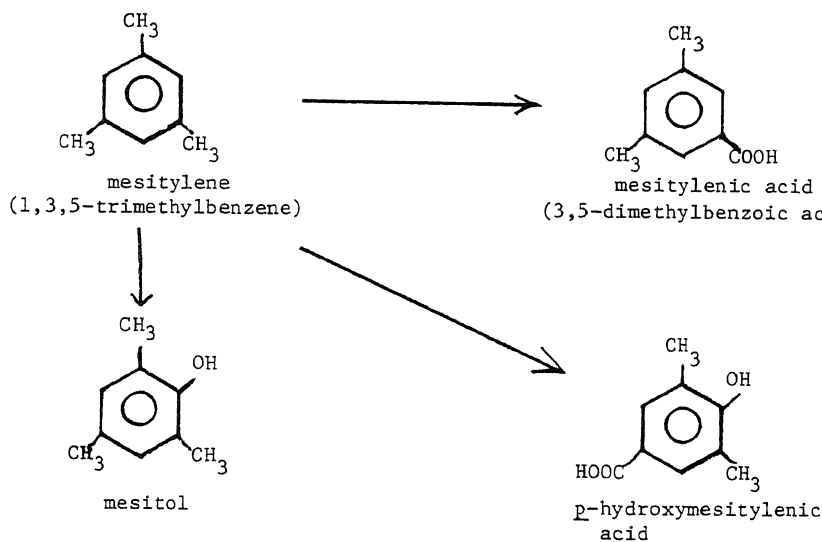
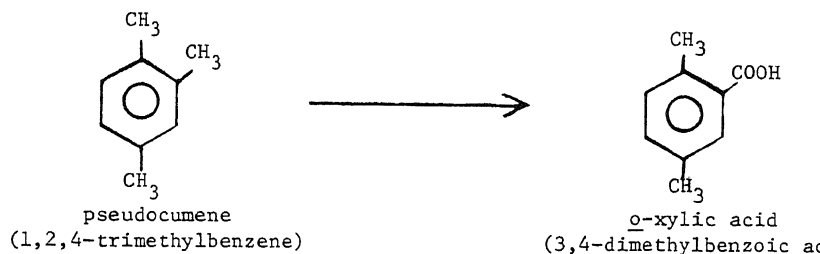


FIGURE 5-3. Metabolic pathways for trimethylbenzenes.

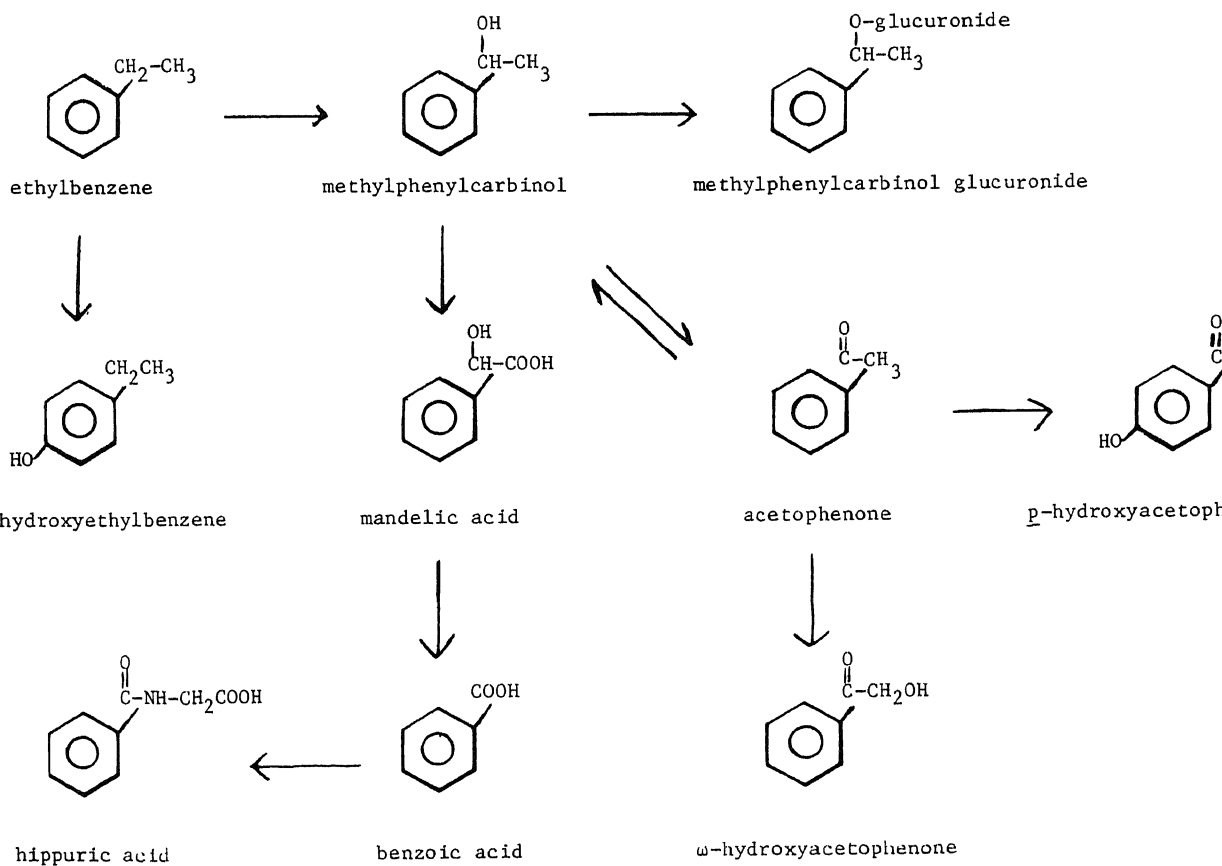


FIGURE 5-4. Metabolic pathways for ethylbenzene.

approximately 4% of a percutaneous dose (Dutkiewicz and Tyras, 1967) are converted to mandelic acid in humans. Since hippuric acid was not detected as a major metabolite of ethylbenzene in these studies, humans apparently lack the ability to convert mandelic acid to benzoic acid, the precursor of hippuric acid.

A comparison of results from in-vitro studies with those from in-vivo studies reveals that ethylbenzene is converted by a cytochrome P-450 enzyme in rat liver microsomes to both the R-(+) and S-(-) isomeric forms of methylphenylcarbinol (McMahon and Sullivan, 1969). In untreated rats, the ratio of the R-(+) to the S-(-) isomers formed is approximately 4:1. The difference is less in rats that have been pretreated with phenobarbital. The fact that S-(+) α -deuterated ethylbenzene is converted to R-(+) α -d-methylphenylcarbinol demonstrates that the configuration of the substrate is retained during hydroxylation.

Most of the R-(+) isomer of methylphenylcarbinol is converted to its glucuronide and excreted into the urine. But the S-(-) isomer undergoes extensive oxidation to mandelic acid and to acetophenone (McMahon and Sullivan, 1969). In turn, acetophenone may be reduced back to S-(-) methylphenylcarbinol by a dehydrogenase in the soluble fraction of the liver and then oxidized to mandelic acid. It also undergoes oxidation by microsomal enzymes in the liver to α -hydroxyacetophenone. In rats, acetophenone is additionally oxidized to benzoic acid, which is excreted into urine as hippuric acid (Kiese and Lenk, 1974), but the mechanism of this reaction is not clear. Ohtsuji and Ikeda (1971) observed that mandelic acid increases the excretion of both hippuric acid and phenylglyoxylic acid in the urine of rats, whereas phenylglyoxylic acid does not increase the excretion of either compound. This finding suggests that mandelic acid, but not phenylglyoxylic acid, is decarboxylated to a precursor of benzoic acid.

Acetophenone also undergoes meta and para hydroxylation (Kiese and Lenk, 1974). The conversion of ethylbenzene to p-hydroxyethylbenzene presumably occurs through the formation of its 3,4-epoxide followed by a nonenzymatic rearrangement. Like toluene, the hydrogen in the para position undergoes a shift to the meta position. It is evident, however, that the presumed arene oxide intermediates cannot be very stable because none of the other kinds of metabolites frequently formed from arene oxides have been isolated from urine. For example, there is no evidence for the presence of dihydrodiols, catechols, or mercapturic acids.

Styrene

Absorption. Styrene readily enters the body by the inhalation route or by absorption from the gastrointestinal tract and through the skin (Browning, 1965; Gerarde, 1960). Dutkiewicz and Tyras (1968b)

have estimated that pure liquid styrene is absorbed through human skin at an approximate rate of 9 to 15 mg/cm²/hr. For humans, exposure of the hands to liquid styrene for a few minutes could be equivalent to an inhalation exposure to an atmosphere containing 12 ppm for 8 hr.

Disposition. Styrene is distributed rapidly to all tissues in the body, especially to adipose tissue. In fact, the ratio of styrene in fatty tissue to styrene in brain tissue in rats after an inhalation exposure of 7.9 μ mol/liter for 4 to 10 weeks may be as high as 25:1 or 30:1 (Savolainen and Pfaffli, 1978). The same investigators observed similar ratios for styrene in lipids to styrene in blood.

Pharmacokinetic studies with mice (Bergman, 1979) and with rats and humans (Ramsey and Young, 1978) have shown that the disposition of styrene may be simulated by a two-compartment model. Ramsey and Young (1978) have calculated that humans exposed to an atmosphere containing 80 ppm of styrene absorb the substance at an approximate rate of 100 mg/hr. Since the concentration of styrene in blood approaches a nearly constant concentration of 0.9 μ g/ml after a 6-hr exposure, it may be calculated that the total body clearance of styrene in humans is approximately 12.7-26.5 ml/min/kg (Ramsey et al., 1980). This rate is similar to the estimated average hepatic blood flow in humans (approximately 20 ml/min/kg).

These calculations suggest that nearly all of the styrene in blood is cleared as it passes through the liver. After cessation of the exposure, the concentration of styrene in blood declines rapidly; the half-life of the α phase is approximately 0.58 ± 0.08 hr, whereas the half-life of the β phase is approximately 13.0 ± 0.7 hr (Ramsey and Young, 1978; Ramsey et al., 1980). Because a steady state is not completely reached even after a 6-hr exposure to styrene, it is difficult to establish with precision the relative areas under the curve for the α and β phases. It is evident, however, that a significant proportion of the total area under the curve is associated with the α phase, an estimate that supports the view that styrene is rapidly eliminated from humans. Moreover, less than 3% of the absorbed styrene is exhaled, even though styrene is rapidly absorbed by inhalation.

In pharmacokinetic studies of styrene in rats exposed to an atmosphere containing 80 ppm styrene, Ramsey and Young (1978) estimated that styrene was absorbed at approximately 2.85 mg/hr. By the end of a 6-hr exposure, the concentration of styrene in blood had reached an almost constant value of approximately 0.8 μ g/ml. From these values, the total body clearance of styrene in the rats can be estimated to be approximately 59 ml/min. Unfortunately, the authors did not report the size of the rats. If they weighed 300 g, the total body clearance would exceed the hepatic blood flow in rats (~ 75 ml/min⁻¹/kg⁻¹) (Pang and Gillette, 1978). Thus, there may be extrahepatic elimination of styrene in

rats. After withdrawal of styrene, the half-life of the α phase is approximately 0.26 hr, whereas that of the β phase was approximately 2.76 hr. Since the initial concentrations of the β phase were greater than those for the α phase, the concentration of styrene attained after a 6-hr exposure is very close to the steady-state concentration.

When a substance that is distributed into a two-pool system is constantly infused until a steady-state is attained and then the infusion is stopped, the concentration of the substance in blood will decline biexponentially. Extrapolation of the β -phase of the decline in the concentration at the time the infusion was stopped provides a value (B_0). The ratio of the B_0 value to the steady-state concentration of the substance should be the same as the ratio of the area under the curve of the β -phase to the total area under the curve of the substance as the substance is rapidly injected intravenously. Application of this pharmacokinetic technique reveals that when a dose of styrene is administered intravenously, only approximately 10% of the total area under the curve is due to the β phase. This gives further credence to the view that styrene is cleared from the body very rapidly and that the rate of clearance may be limited by the hepatic blood flow.

Ramsey and Young (1978) and Withey and Collins (1979) report that the elimination of styrene from rats is dose dependent. The steady-state concentrations of styrene in blood achieved after high inhalation doses (1,200 ppm) were considerably greater than those predicted from the low dose (80 ppm). The authors' conclusion that the "clearance mechanism" may become saturated at the high dose is probably valid, but it has not been proved conclusively. It is possible that the high doses may have caused a decrease in hepatic blood flow and thereby have decreased the clearance. Results obtained from pharmacokinetic studies of intravenously administered styrene in rats are consistent with these results (Withey, 1978).

Studies in mice have shown that styrene is rapidly absorbed via the inhalation route and is eliminated by metabolic processes. Bergman (1979) showed that the rate of unchanged styrene elimination by exhalation fits the following equation:

$$\% \text{ dose exhaled/min} = 0.0186 e^{-0.0447t} + 0.0093 e^{-0.0075t}$$

Upon integration, this equation becomes:

$$\% \text{ dose exhaled} = 0.42 + 3.72 = 4.14$$

Inspection of the equation reveals that the pharmacokinetics of styrene in mice is similar to that in rats. But the relative distribution of the areas under the curve suggests that the ratio of the rate constant of elimination to the rate constants of distribution

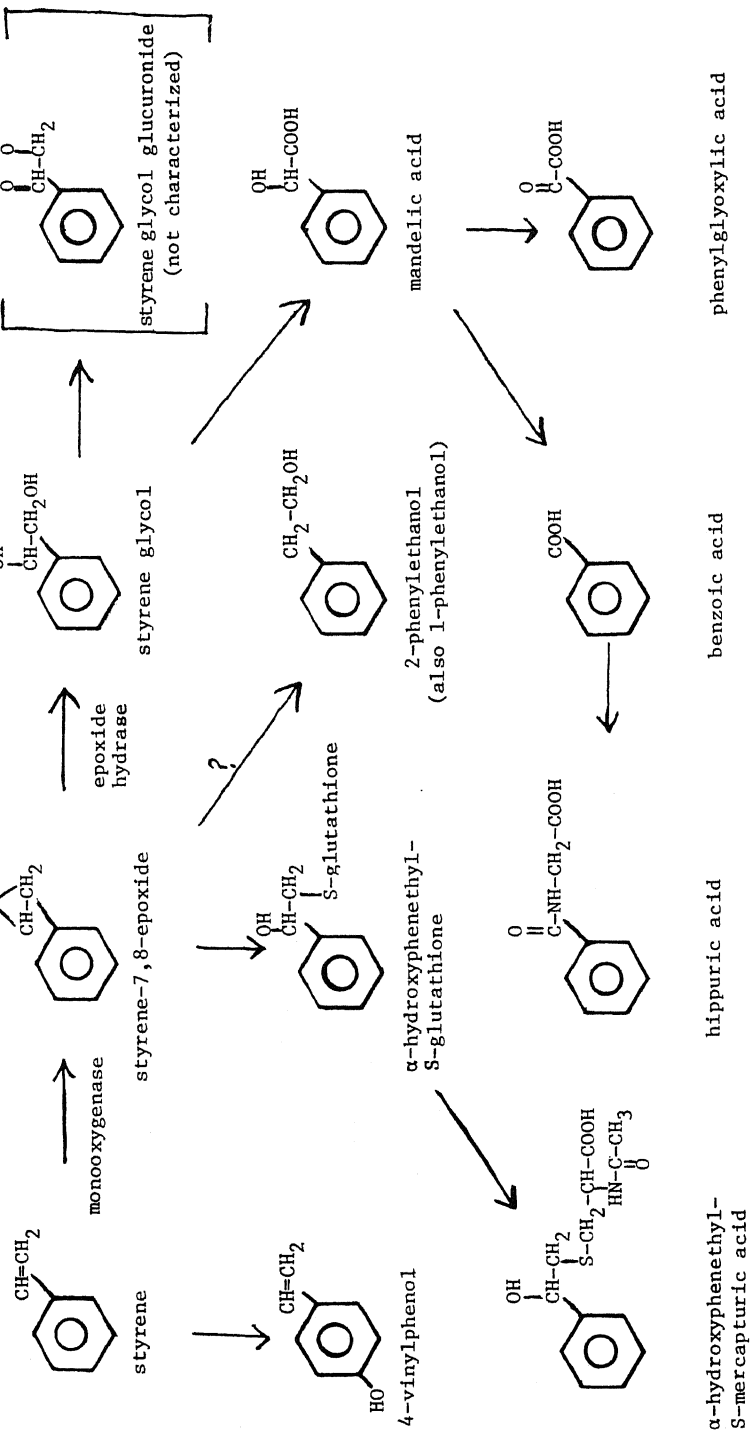
may be less in mice than in rats. Unfortunately, the data provided by Bergman (1979) do not permit an estimate of the total body clearance.

Figure 5-5 shows the pathways of styrene metabolism. In rats, approximately 50% of a dose of styrene is excreted into urine as mandelic acid, phenylglyoxylic acid, hippuric acid, α -hydroxyphenethyl-S-mercapturic acid, and an unidentified glucuronide, which is presumed to be phenethyl glucuronide (James and White, 1967; Ohtsuji and Ikeda, 1971). Very small amounts of the dose of styrene are also excreted as 4-vinylphenol and as 1- and 2-phenylethanol. Approximately 72% of a dose of styrene administered to rabbits has been isolated from the urine as mandelic acid (32%) and hippuric acid (40%). Another 5% of the dose has been isolated as the α -hydroxyphenethyl-S-mercapturic acid and 6% as the unidentified glucuronide (James and White, 1967). In studies with humans, Bardodej and Bardodejova (1970) isolated approximately 95% of a retained dose as mandelic acid and phenylglyoxylic acid. Apparently very little, if any, hippuric acid or mercapturic acid is formed in humans.

The major pathway of styrene metabolism in mammals is mediated through the formation of styrene-7,8-epoxide (Leibman and Ortiz, 1969, 1970) (Figure 5-5). In turn, the epoxide reacts either with glutathione to form a conjugate that is excreted in urine as mercapturic acid or with water to form styrene glycol. The glycol may be formed either enzymatically through the action of epoxide hydratase or nonenzymatically. The enzyme acts equally well with the R and S forms of the styrene epoxide (Jerina, unpublished results). Styrene glycol is then converted to a glucuronide or is oxidized to mandelic acid and phenylglyoxylic acid. In rats and rabbits, it is further converted to benzoic acid.

Benzoic acid, which is eventually excreted in urine as hippuric acid, is formed through a mechanism that is not yet understood. Since hippuric acid is formed in rats from mandelic acid, but not from phenylglyoxylic acid (Ohtsuji and Ikeda, 1971), it appears that benzoic acid may result mainly from decarboxylation of mandelic acid. The data reveal that considerably less hippuric acid is formed from mandelic acid than from either styrene or styrene glycol, which suggests either that there is another mechanism for the formation of benzoic acid or that the mandelic acid inhibits the formation or excretion of hippuric acid. Both mandelic acid and phenylglyoxylic acid appear to decrease the excretion of endogenous glucuronides into rat urine. Since little hippuric acid is formed from styrene in humans, it is apparent that humans are deficient in the enzyme that catalyzes the formation of benzoic acid from styrene metabolites.

Pretreatment of rats with phenobarbital increases the fraction of the dose (455 mg/kg) of styrene that is excreted in urine within 10 hr after administration. Although this increase may be due



ETC/UEP 5-5 Metabolic pathways for stressors

partially to an increase in hepatic blood flow caused by prior administration of phenobarbital, it is more likely that the major effect of the pretreatment is an increased activity of the cytochrome P-450 enzyme that catalyzes the formation of styrene epoxide. For this to be true, however, the concentration of styrene attained in hepatic sinusoids during the absorption of large doses of styrene would have to be high enough to saturate the cytochrome P-450, thereby markedly increasing the initial clearance of styrene by the liver. Induction of the cytochrome P-450 enzyme by phenobarbital would thus decrease the fraction of the dose that enters the systemic circulation after intraperitoneal administration of styrene and increase the clearance of styrene while the concentration of styrene in systemic blood is high. Although the clearance of low concentrations of styrene appears to be limited by the rate of hepatic blood flow, it is questionable whether the effect of phenobarbital on the blood flow would be great enough to affect significantly the metabolism of low, inhaled doses of styrene.

In recent years, there has been considerable interest in the disposition of styrene epoxide, which has been shown to be mutagenic in bacteria and to combine with several other nucleophiles in addition to glutathione. However, studies on the disposition of preformed styrene epoxide are of doubtful value because the pharmacokinetics of preformed styrene epoxide probably differ markedly from the pharmacokinetics of styrene epoxide that has formed in the liver and other tissues of the body. For example, 10 hr after a 527 mg/kg dose of styrene oxide was administered to rats, approximately 15% of the dose was excreted in the urine as hippuric acid, phenylglyoxylic acid, and mandelic acid (Ohtsuji and Ikeda, 1971). In contrast, approximately 0% of similar doses of styrene and styrene glycol were excreted.

-Methyl styrene

Absorption. Nothing is known about the absorption and distribution of this compound in mammals, but there is no reason to believe that the rates of absorption and the pattern of distribution of this compound would differ markedly from those of styrene.

Disposition. As shown in Figure 5-6, α -methyl styrene is excreted in the urine of humans mainly as α -hydroxy- α -methylphenylacetic acid (α -methylmandelic acid) (Bardodej and Bardodejova, 1970). Similar to the pattern of the metabolism of styrene, α -methyl styrene is probably converted first to its epoxide (α -methyl styrene epoxide) and then to a diol (α -methyl styrene diol), which is oxidized to the acid.

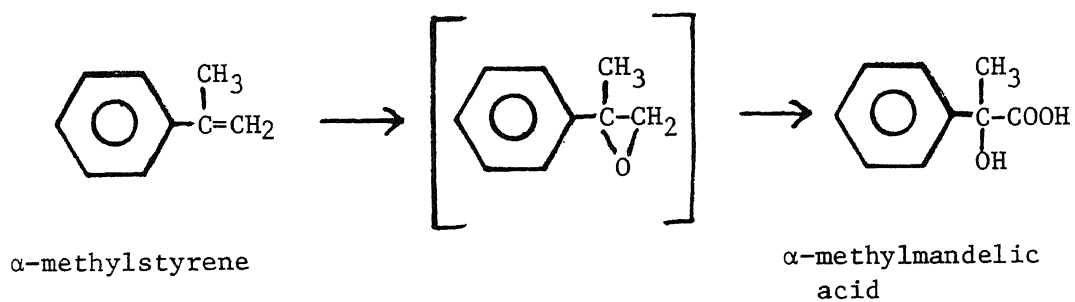


FIGURE 5-6. Metabolic pathways for α -methylstyrene.

Cumene

Absorption. Nothing is known about the absorption and distribution of cumene in mammals. It seems likely, however, that it can enter the body via inhalation and via absorption from the gastrointestinal tract and through the skin at rates similar to those obtained with ethylbenzene.

Disposition. As shown in Figure 5-7, cumene is excreted in the urine of rabbits as the glucuronides of 2-phenylpropan-2-ol (40%), 2-phenylpropan-1-ol (hydratropyl alcohol) (25%), and α -phenylpropionic acid (hydratropic acid) (25%) (Robinson et al., 1955).

Interactive Mechanisms

Various forms of cytochrome P-450 enzymes in the liver and other tissues are known to catalyze the metabolism of not only alkyl benzenes but also a multitude of other foreign compounds, including drugs. Each form of cytochrome P-450 has its own range of substrate specificity (Haugen et al., 1975) and kinetic characteristics. Thus, the total body clearance of a given substance represents the sum of the contributions of the individual forms. Unfortunately, because the individual forms of cytochrome P-450 in human tissues have not been isolated, their substrate specificities and their kinetic characteristics for any given substrate are unknown. Nevertheless, the dose-dependency of the total body clearance of styrene (and presumably other alkyl benzenes) reported by Ramsey and Young (1978) suggests that some forms of cytochrome P-450 that catalyze the conversion of styrene to its epoxide approach saturation at the administered doses of styrene. Therefore, large doses of styrene should inhibit to some extent the metabolism of the drugs and other foreign compounds that are also metabolized by these forms of cytochrome P-450.

Whether inhibition of the metabolism of the other foreign compounds exacerbates or diminishes their toxicity depends on whether the toxicity is caused by the parent substance or by a metabolite of the substance. For example, Snyder and Kocsis (1975) suggest that large doses of toluene prevent the toxic effects of benzene by inhibiting the conversion of benzene to toxic metabolites. Moreover, Ciuchta et al. (1979) report that toluene decreases the formation of the hemoglobin-carbon monoxide complex derived from dichloromethane by slowing the conversion of dichloromethane to carbon monoxide. In these instances, high doses of the alkyl benzenes decrease the toxicity. But the possibility that high doses of these substances potentiate the toxicity of other drugs should not be neglected.

The mammalian kidney contains one or more active transport systems that accelerate the renal clearances of many anionic foreign compounds (Weiner, 1973). When the foreign compound is

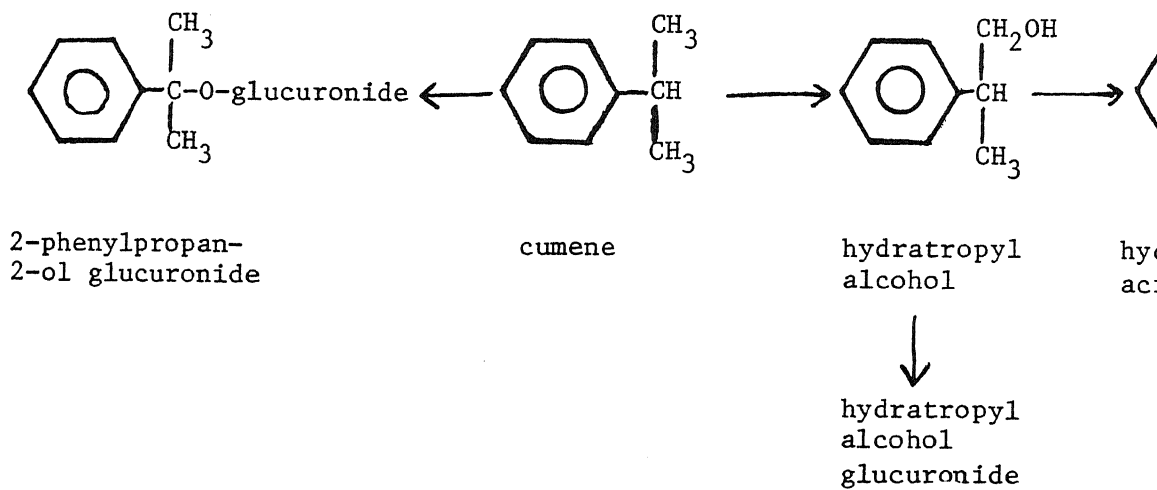


FIGURE 5-7. Metabolic pathways for cumene.

acid, the ionized form is excreted into the lumen of the tubule where it equilibrates with its nonionized form, depending on the pKa of the weak acid and the pH of the ultrafiltrate (Weiner, 1973). If the nonionized form is sufficiently lipid-soluble, it passes from the lumen of the tubule back into the blood. Thus, weak acids may interact with the transport systems even when the rate of clearance by the kidneys appears to be low. Moreover, there are other transport systems that accelerate the reabsorption of endogenous substances such as uric acid. Like enzymes, both types of transport systems may be saturated at high concentrations of anionic foreign compounds and may therefore inhibit the transport of other anionic substances. Thus, probenecid [*p*-(dipropylsulfamyl)benzoic acid] inhibits the renal excretion of penicillin but accelerates the excretion of uric acid, even though it is itself poorly cleared by human kidneys.

Among the anionic substances actively excreted by the kidneys are derivatives of hippuric acid, phenacetic acid, and conjugates of glucuronic acid and sulfate (Weiner, 1973). Although certain derivatives of benzoic acid (*p*-aminobenzoic acid) and mandelic acid (phenylmandelic acid) are cleared at about the same rate as creatinine and inulin in dogs and humans (Smith *et al.*, 1945), it is still possible that these substances interact with the transport systems in kidney tubules. Thus, at sufficiently high concentrations of the metabolites of the alkyl benzenes would be expected to inhibit the excretion of other anionic foreign compounds.

Repeated administration of large doses of foreign compounds eventually results in large accumulations of cytochrome P-450 enzymes, often termed "drug-metabolizing enzymes" in tissues. Savolainen and Li (1978) reported that intermittent exposure of rats to styrene at doses of 300 ppm, 6 hr/day, 5 days/week for more than 4 weeks raises the steady-state concentration of styrene in adipose tissue. This finding raises the possibility that styrene may enhance its own metabolism. However, this hypothesis has not been tested by direct kinetic studies of styrene metabolism in rats or in other animal species. There is no evidence that chronic administration of large doses of other alkyl benzenes significantly alters either the rate of metabolism or the metabolism of other foreign compounds. For example, *p*-xylene does not induce its own metabolism (Harper *et al.*, 1977). It is uncertain whether the lack of an inducing effect is due to an inherent inability to induce the synthesis of cytochrome P-450 or to rapid elimination of the alkyl benzenes.

p-Tolualdehyde decreases the amount of cytochrome P-450 in the liver of rabbits. Although the activity of these enzymes in the lung only contributes very little to the total body clearance of foreign compounds, decreases in cytochrome P-450 may decrease the toxicity of compounds such as 4-ipomeanol [1-(3-furanyl)-4-hydroxy-1-pentanone],

which are converted to toxic metabolites in the lung (Boyd *et al.*, 1978). Moreover, many allylic compounds are known to decrease the amount of cytochrome P-450 in the liver of rats, particularly after the animals are pretreated with phenobarbital (Levin *et al.*, 1973). There have been no adequate studies to determine if styrene produces similar effects. Although the intraperitoneal administration of styrene oxide to rats results in the destruction of liver microsomal cytochrome P-450 (Parkki *et al.*, 1976), there is no evidence to suggest that similar destruction would occur at the low doses of styrene that are ordinarily encountered.

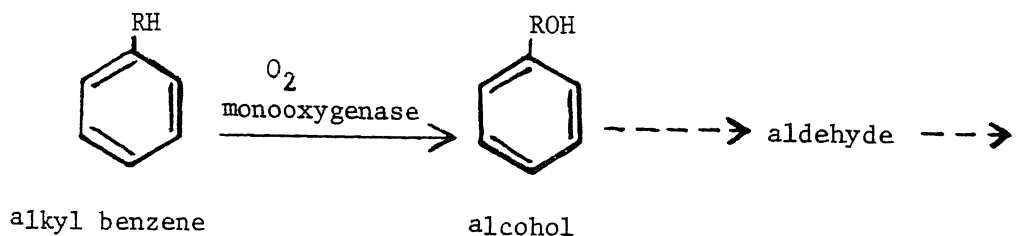
METABOLISM IN NONMAMMALIAN SPECIES

Microbial Metabolism of Alkyl Benzenes

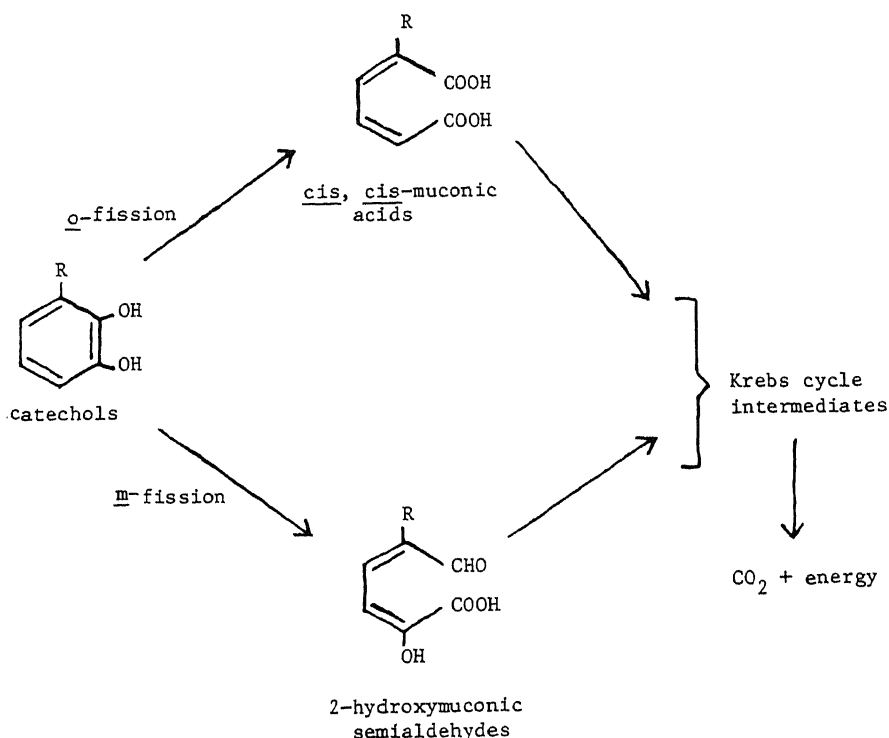
The pathways of xenobiotic metabolism in higher organisms are directed primarily towards the elimination of potentially hazardous lipophilic compounds from the tissues. In contrast, the pathways in bacteria permit the formation of degradation products that can ultimately enter the major metabolic channels (e.g., Krebs cycle, fatty acid oxidation). In this manner, the products serve as important sources of energy.

The remarkable diversity of the xenobiotic metabolic pathways found in microbes has been discussed in several reviews (Gibson, 1971; Hayaishi, 1966; National Academy of Sciences, 1972). Because they are extremely versatile, microbes can metabolize alkyl benzenes and other xenobiotics through a variety of unique pathways. They can also catalyze many of the same reactions that occur in higher organisms. Most enzymes involved in these pathways are observed only when the substrate constitutes the sole source of carbon for the microbe, i.e., the enzymes are induced in response to the substrate. The pathways vary with the compound and the bacterial species.

Like higher organisms, aerobic bacteria rely on a variety of oxidative enzymes to catalyze the initial attack on the alkyl benzene. In some cases, this involves monooxygenases in an action similar to that for the cytochrome P-450-mediated enzymes in mammals. The enzymes catalyze predominantly the oxidation of the aliphatic ring substituents:



while simultaneously using the released energy (National Academy of Sciences, 1972). Enzymes that catalyze this reaction are classified as dioxygenases (Hayaishi, 1966). They are non-heme iron-containing enzymes that catalyze the incorporation of both atoms of molecular oxygen into the substrate during the ring-opening reaction. The ability of microorganisms to catalyze fission of the aromatic nucleus is dependent upon the presence in the ring of at least two hydroxyl groups that are typically ortho to one another. Thus, the catechols produced by dehydrogenation of the dihydrodiols serve as good substrates for the enzymes that catalyze ring fission. The rings may be opened by either ortho or meta cleavage to yield the corresponding cis-cis-muconic acids or 2-hydroxymuconic semialdehydes, respectively (Dagley, 1971, 1972; Feist and Hegeman, 1969). These are subsequently transformed into a variety of Krebs cycle intermediates (e.g., succinate, pyruvate, and acetate), which are completely oxidized to carbon dioxide:



Because of their ability to effect the complete oxidation of aromatic hydrocarbons, microbes are important determinants of the longevity of alkyl benzenes.

Toluene. Studies with *Pseudomonas aeruginosa* by Kitagawa (1968) and Nozaka and Kusunose (1968) suggested that the primary metabolic

pathway for toluene is oxidation to benzoic acid through benzyl alcohol and benzaldehyde (Figure 5-8). Subsequently, Claus and Walker (1964) reported that toluene in washed suspensions of Pseudomonas spp. and Achromobacter spp. was metabolized to 3-methylcatechol, acetic acid, and pyruvic acid. In studies to elucidate the nature of intermediates in the pathway from toluene to 3-methylcatechol, Gibson et al. (1970) observed that toluene in a suspension with a mutant strain (39/D) of Pseudomonas putida yielded (+)-cis-2,3-dihydroxy-1-methylcyclohexa-4,6-diene as its initial degradation product. The absolute stereochemistry of this product has been elucidated by Kosal et al. (1973). Gibson et al. (1970) also established that the cis-dihydrodiol from toluene was enzymatically dehydrogenated to 3-methylcatechol by P. putida. In subsequent attempts to purify and characterize the enzyme responsible for the reaction, Rogers and Gibson (1977) determined that the enzyme was composed of four identical subunits with molecular weights of 27,000 and had a specific requirement for NAD⁺. The investigators also reported that the activity of the enzyme was specific for cis-dihydrodiols although a fairly broad degree of substrate specificity was exhibited for this type of compound.

Subsequent metabolism of 3-methylcatechol appears to proceed mainly through meta fission of the aromatic ring to yield 2-hydroxy-6-oxo-2,cis-4,cis-heptadienoic acid, which can be further converted to acetate, acetaldehyde, and pyruvate (Bayly et al., 1966; Dagley et al., 1964).

The microbial metabolism of toluene is summarized in Figure 5-8.

Xylenes. Bacteria known to grow with p- or m-xylene as their sole carbon source oxidize these substrates to the corresponding toluic acids (Bayly et al., 1966; Davey and Gibson, 1974; Omori and Yamada, 1969; Omori et al., 1967). However, Skryabin et al. (1978) have presented evidence that p-xylene may be oxidized to p-toluic acid, not only by molecular oxygen through an oxygenase mechanism but also by an anaerobic mechanism in which the oxygen is derived from water. Initial evidence to support this was supplied by their observation that oxidation of the methyl groups of p-xylene by Pseudomonas aeruginosa and Nocardia sp. was not related to the level of aeration in the culture media. Indeed, these two species could produce p-toluic acid from p-xylene under anaerobic (nitrogen or helium) conditions.

Omori and Yamada (1970a, b) reported that a strain of Pseudomonas aeruginosa also produced and oxidized 4-methylcatechol when grown on p-xylene, whereas the same strain produced 3-methylsalicylic acid as the major product from m-xylene. Subsequently, Davey and Gibson (1974) established that 3- and 4-methylcatechols were produced by m- and p-xylene, respectively, in their studies with the Pxy strain of Pseudomonas (Figures 5-9 and 5-10). These investigators suggested that these catechols were the major substrates for

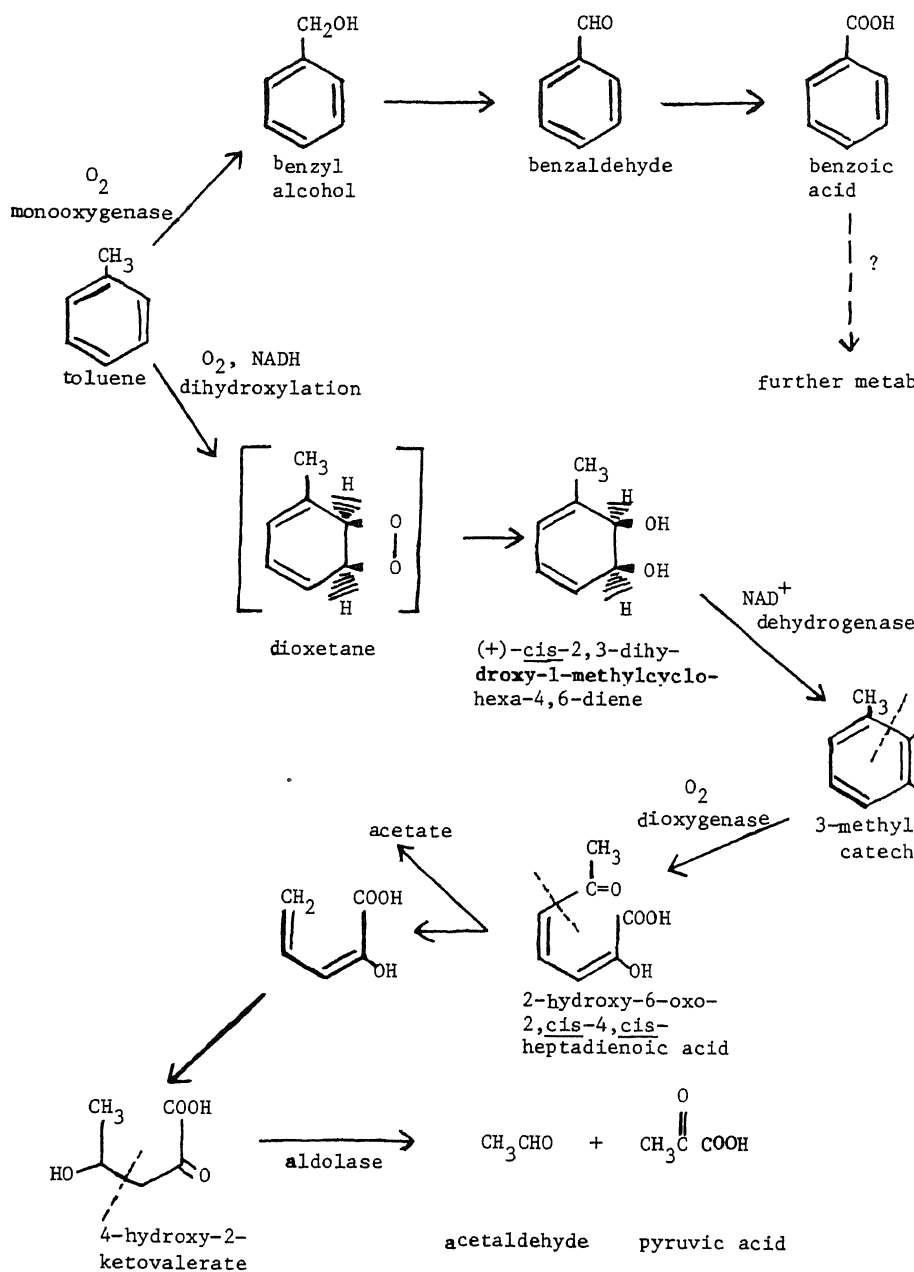


FIGURE 5-8. Microbial metabolism of toluene.

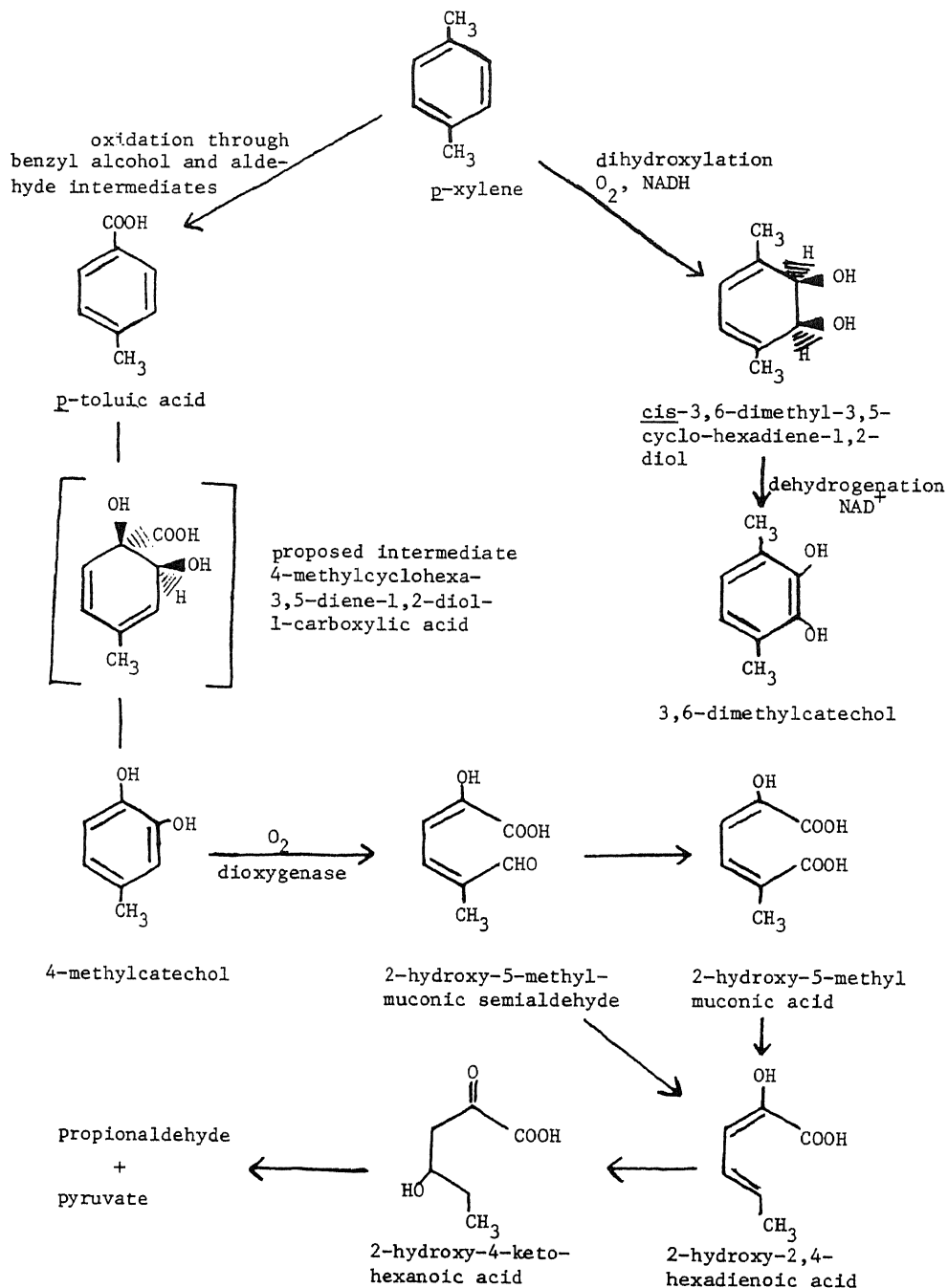


FIGURE 5-9. Microbial metabolism of p-xylene.

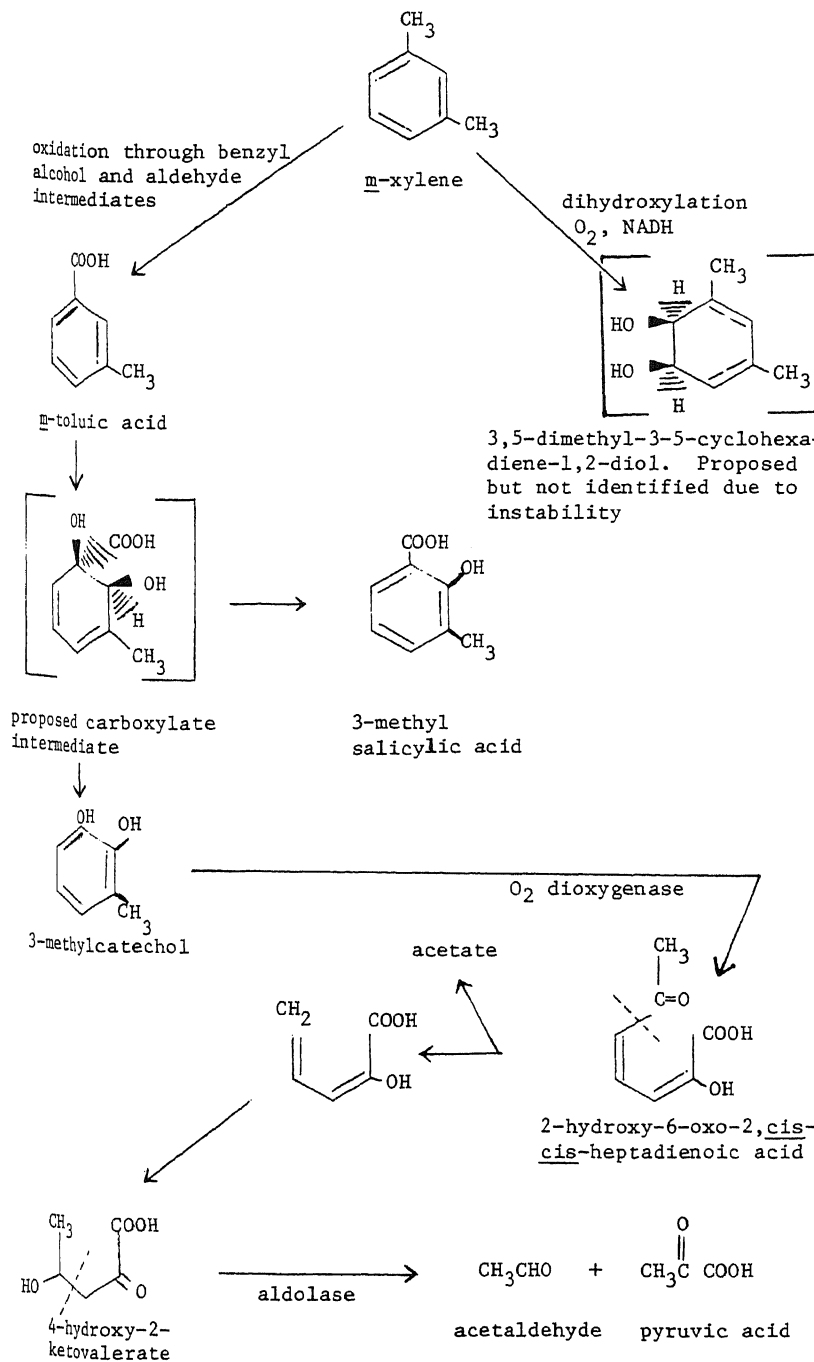


FIGURE 5-10. Microbial metabolism of m-xylene.

subsequent ring fission and that they were produced from the m- and p-toluic acids through the unstable 3- and 4-methylcyclohexa-3,5-diene-1,2-diol-1-carboxylic acids, respectively (Figure 5-9). Support for this suggestion comes from the finding of Reiner and Hegeman (1971) that a mutant strain of Alcaligenes eutrophus oxidized m-toluic acid to a compound tentatively identified as 3-methylcyclohexa-3,5-diene-1,2-diol-1-carboxylic acid, which was converted to 3-methylcatechol by an enzyme from another strain of this organism. Moreover, they suggested that the carboxylic acid intermediate could lead to 3-methylsalicylic acid, which was found to be a product of m-xylene degradation in Pseudomonas sp.

Davey and Gibson (1974) report that both 3- and 4-methylcatechols are rapidly metabolized by the Pxy strain of Pseudomonas. The major product of 4-methylcatechol is 2-hydroxy-5-methylmuconic semialdehyde. The authors suggest that analogous fission products are formed from the 3-methylcatechol.

In addition to the degradative pathways initiated by oxidation of the methyl groups, the 39/D strain of Pseudomonas putida was found to oxidize p-xylene to cis-3,6-dimethyl-3,5-cyclohexadiene-1,2-diol (cis-p-xylene dihydrodiol) (Gibson et al., 1974; see Figure 5-9). m-Xylene was oxidized to a highly unstable compound with characteristics similar to 3,5-dimethyl-3,5-cyclohexadiene-1,2-diol. Since the parent strain, when grown in the presence of succinate and p- or m-xylene, produces 3,6- and probably 3,5-dimethylcatechols, it is possible that these two compounds can be formed by dehydrogenation of the corresponding cis-dihydrodiols. Additional ring-fission products from these catechols have not been identified.

In most of these metabolic studies, alkyl benzenes have been used as the sole source of carbon and energy in the culture medium. The process of biotransformation of aromatic compounds may be different if such studies are conducted during cometabolism with an alternative growth substrate. Thus, when butyrate is used as the source of carbon, p-xylene is oxidized by a culture of Nocardia sp. (strain 1A) to p-hydroxymethylbenzoic acid (Skryabin et al., 1974). Since microorganisms have a variety of growth substrates under most environmental conditions, metabolic pathways probably vary considerably.

Ethylbenzene. Ethylbenzene possesses several sites that are susceptible to oxidative microbial attack. The site of the initial reaction varies with the source and specificity of the enzyme system involved (Figure 5-11). For example, when the microbial species is the 39/D strain of Pseudomonas putida, one major pathway involves initial oxidation to (+)-cis-3-ethyl-3,5-cyclohexadiene-1,2-diol and subsequent NAD⁺-dependent oxidation to the corresponding 2,3-dihydroxy-1-ethylbenzene (Gibson et al., 1973). An alternative pathway of relatively minor importance produces (+)-cis-3-(1-hydroxyethyl)-3,5-cyclohexadiene-

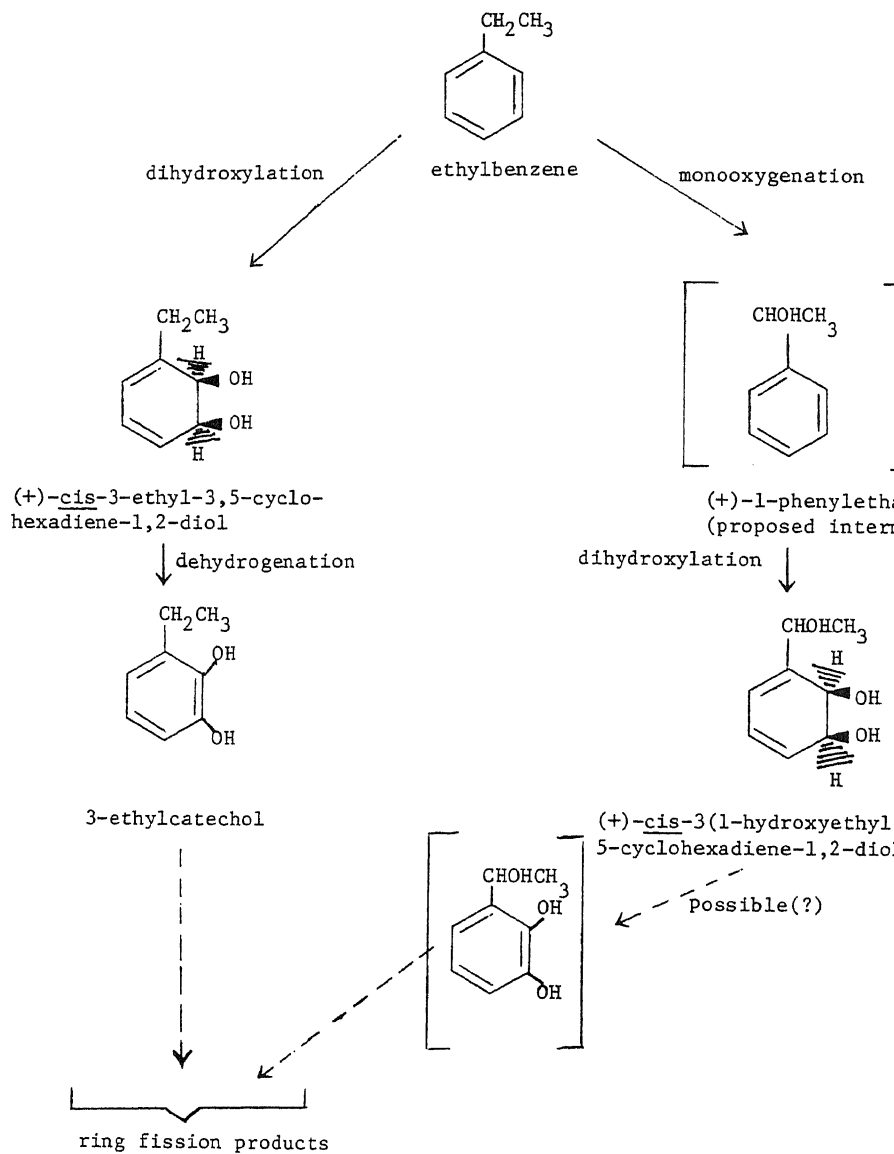


FIGURE 5-11. Microbial oxidation of ethylbenzene.

1,2-diol. This compound is also produced from (+)-1-phenylethanol, which is assumed to be the initial intermediate in this pathway (Gibson et al., 1973).

Styrene. Despite a report by Clifford et al. (1969) that styrene is formed through the decarboxylation of cinnamic acid by several microbial species, Omori et al. (1975) were unable to demonstrate that styrene could serve as the sole carbon source for supporting the growth of several mixed populations of soil microorganisms. Recently, Sielicki et al. (1978) established that some of these mixed populations did utilize the carbon in styrene and that the compound is metabolized by two different mechanisms. One mechanism involves the metabolism of styrene to phenylethanol and phenylacetic acid, whereas the other involves polymerization to low-molecular-weight styrene oligomers (Figure 5-12). The latter reaction might occur spontaneously following microbial metabolism of tert-butylcatechol, an inhibitor of oxidative polymerization that is present in commercial styrene. Clearly, the products of both pathways rapidly undergo further metabolism: approximately 90% and 75% of the 8-¹⁴C-labelled styrene appears as ¹⁴CO₂ within 16 weeks after 0.2% and 0.5% styrene, respectively, are applied to the incubations.

Cumene (Isopropylbenzene)

In one of the few studies of the microbial metabolism of iso-alkyl-substituted aromatic hydrocarbons, Jigami et al. (1975) reported the degradation pathways of isopropylbenzene (cumene) and isobutylbenzene by Pseudomonas acidovorans (strain S449B1) and Pseudomonas putida (strain S107B1) (Figure 5-13). These authors suggest that the iso-alkyl-substituted aromatic nucleus is oxidized to the appropriate 3-substituted catechol through dehydrogenation of the corresponding cis-dihydrodiol intermediate. The major ring cleavage product arising from isopropylbenzene appears to be (+)-2-hydroxy-7-methyl-6-oxooctanoic acid. Unlike most of the ring fission products described for other alkyl benzenes, this is a saturated compound whose formation indicates the existence of an unknown reductive step.

PLANT METABOLISM OF ALKYL BENZENES

There are few data on the metabolism of alkyl benzenes by plants. In the vapor phase, toluene and, to a lesser extent, benzene are absorbed by avocado fruit and are metabolized to both volatile and nonvolatile products (Jansen and Olson, 1969). A small but significant percentage of each is converted to carbon dioxide. Toluene is also synthesized by avocado fruit that have been exposed to ethylene (Jansen, 1964).

In a more comprehensive study, Durmishidze et al. (1974) observed that toluene was absorbed and metabolized by corn and bean seedlings

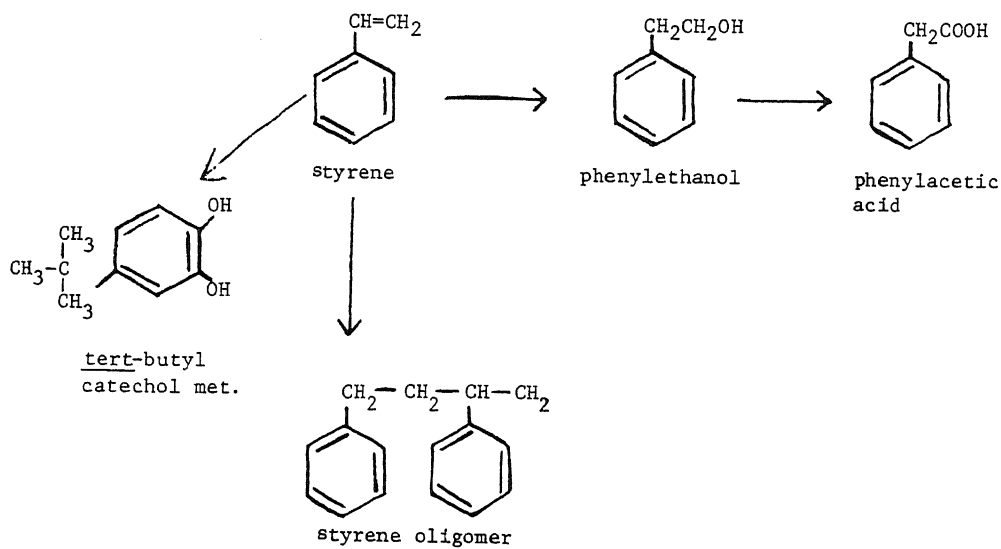


FIGURE 5-12. Microbial metabolism of styrene.

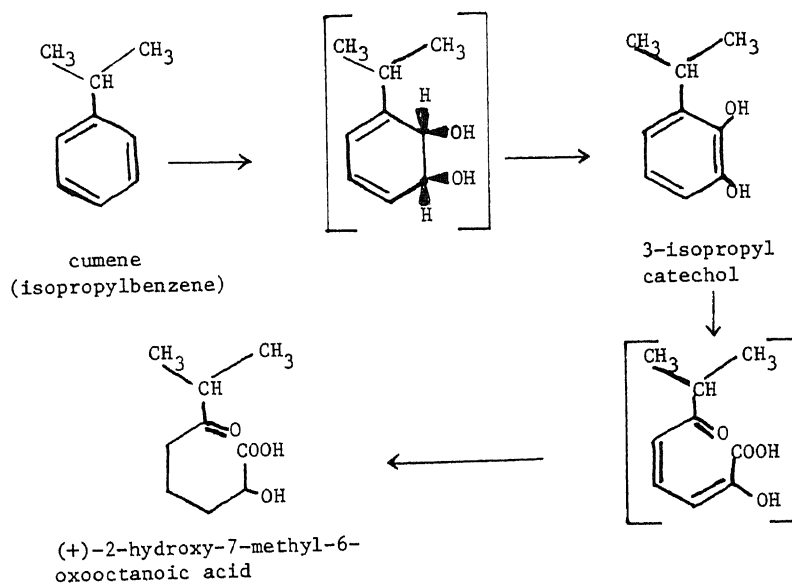
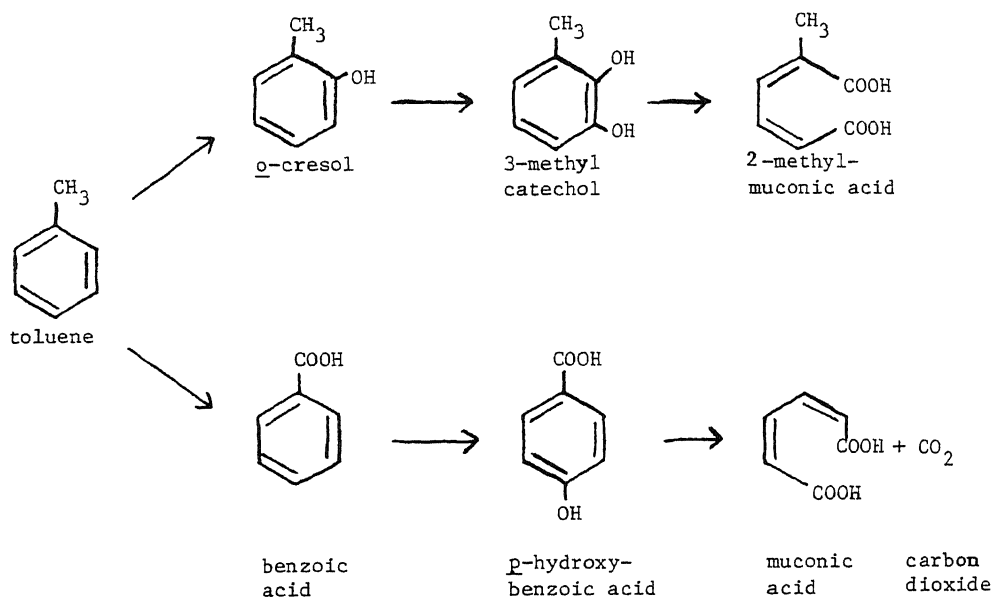


FIGURE 5-13. Microbial metabolism of cumene (isopropylbenzene).

as well as by tea and grape plants. Metabolism occurred in the roots as well as in the leaves and stems of these plants. The side chain of toluene was metabolized to carbon dioxide, whereas approximately 90% of the ring carbons resulting from ring cleavage became incorporated into a variety of low-molecular-weight organic acids, such as glyoxalic, fumaric, succinic, and malic acids, and, to a much lesser extent, into the aromatic amino acids phenylalanine and tyrosine. In corn and grape plants, a very low level of radioactivity appeared in the mono- and disaccharides.

Durmishidze et al. (1974) summarized the oxidation of toluene in plant cells as follows:



In studies of filamentous fungus Cladosporium resinae, Walker and Clooney (1975) found no evidence for metabolism of toluene or p-xylene.

METABOLIC INTERACTIONS OF ALKYL BENZENES IN INSECTS

The patterns of oxidation of alkyl benzene derivatives in insects appear qualitatively similar to those in mammals, although data concerning insect species are very sparse. In an in-vitro study on the metabolism of seven alkyl benzenes by NADPH-fortified 10,000-g supernatants of abdomens of houseflies (Musca domestica) and fat bodies of migratory locusts (Schistocerca gregaria), Chakraborty and Smith (1967) observed that the major oxidation products were alcohols and acids.

Benzoic acid was the only product they detected following incubation with toluene, and the rate at which this compound was oxidized considerably exceeded that for the higher homologs. These investigators provided some evidence that in the higher homologs of the series (e.g., *n*-propyl benzene) oxidation to the secondary alcohol occurred preferentially at the methylene group nearest the aromatic ring and less readily at the penultimate methylene and terminal methyl groups.

In in-vivo studies on the metabolism of toluene and *p*-xylene by adult houseflies (*M. domestica*) and the Egyptian cotton leafworm (*Spodoptera littoralis*), Bakry et al. (1972) observed that the major products were the corresponding benzoic and *p*-toluic acids. The investigators made no attempt to look for conjugated metabolites.

Brattsten and Wilkinson (1973) demonstrated that several alkyl benzenes administered in the diet were potent inducers of microsomal cytochrome P-450 enzymes as well as epoxidase and *N*-demethylase activities in larval midgut tissues of the southern armyworm (*Prodenia eridania*). At concentrations of 13.5 μ mol/g of diet, induction increased with accelerated substitution of the methyl group in the aromatic ring. Toluene had little or no effect. Maximal activity was observed with pentamethylbenzene. In the xylenes, inducing activity increased in the following order: meta < para < ortho. For all compounds tested, the level of induction increased with the concentration of the inducer and the time of exposure. Subsequent studies confirmed the inducing action of xylene and several other solvent mixtures that are frequently used in commercial insecticide formulations (Brattsten and Wilkinson, 1977). These studies suggested that their capacity to cause induction might protect treated insects from the insecticidal component in the formulation.

CONCLUSIONS

Mammals

The principle metabolic pathways of the alkyl benzenes in mammals have been known for many years. Despite the plethora of studies on the metabolism of these substances, few studies have been designed to determine whether any of their biological effects are mediated by their metabolites. Indeed, the studies on the mutagenic effects of styrene epoxide on *Salmonella typhimurium* (Busk, 1979; Watabe et al., 1978) provide the only clear evidence that any of the intermediary metabolites of these compounds are toxic. Unfortunately, it is not clear if the mutagenic effects of styrene observed in these studies were due solely to styrene epoxide. Without such knowledge, it is difficult to evaluate the ways in which metabolism affects the toxicity of the alkyl benzenes or the extent to which differences in the incidence or severity of toxicity among species is due to interspecific differences in metabolism.

Nonmammalian Species

The limited information available indicates that alkyl benzene can be metabolized by a variety of nonmammalian species. The metabolic pathways in insects appear to be quite similar to those reported in mammals. Because the microsomal oxidase systems in a wide variety of vertebrate and invertebrate organisms are similar, the metabolic pathways in fish, birds, reptiles, etc., should also prove to be qualitatively similar, i.e., the major pathways are likely to involve initial oxidation of the alkyl moiety of the compound and subsequent conjugation prior to excretion.

In contrast, metabolism by microbial species and by higher plants involves cleavage of the aromatic ring in addition to side-chain oxidation and leads ultimately to the formation of a variety of straight-chain acids, which can be utilized as a source of carbon and energy production. As a result, it may be assumed that alkyl benzenes will be degraded rapidly by microbial species and that they will probably not accumulate to any significant extent under most environmental conditions.

REFERENCES

- Arató Sugár, E. 1968. (English summary) The toluol concentration in the expired air. *Egeszsegtudomány* 12:247-252.
- Åstrand, I. 1975. Uptake of solvents in the blood and tissues of man. A review. *Scand J. Work Environ. Health* 1:199-218.
- Åstrand, I., H. Ehrner-Samuel, and P. Ovrum. 1972. Toluene exposure. I. Concentration in alveolar air and blood at rest and during exercise. *Work Environ. Health* 9:119-130.
- Bakke, O. M., and R. R. Scheline. 1970. Hydroxylation of aromatic hydrocarbons in the rat. *Toxicol. Appl. Pharmacol.* 16:691-700.
- Bakry, N. M., H. M. Younis, and M. E. Elderfrawi. 1972. Biochemical oxidation of methyl group of toluene and its para-substituted derivatives in the housefly and the Egyptian cotton leafworm. *Z. Angew. Entomol.* 70:237-243.
- Bardodej, Z., and E. Bardodejova. 1970. Biotransformation of ethyl benzene, styrene, and alpha-methylstyrene in man. *Am. Ind. Hyg. Assoc. J.* 31:206-209.
- Bayly, R. C., S. Dagley, and D. T. Gibson. 1966. The metabolism of cresols by species of Pseudomonas. *Biochem. J.* 101:293-301.
- Bergman, K. 1979. Whole-body autoradiography and allied tracer techniques in distribution and elimination studies of some organic solvents: Benzene, toluene, xylene, styrene, methylene chloride, chloroform, carbon tetrachloride and trichloroethylene. *Scand. J. Work Environ. Health* 5(Suppl.1): 1-263.
- Boyd, M. R., L. T. Burka, B. J. Wilson, and H. A. Sasame. 1978. In vitro studies on the metabolic activation of the pulmonary toxin, 4-ipomeanol, by rat lung and liver microsomes. *J. Pharmacol. Exp. Ther.* 207:677-686.
- Brattsten, L. B., and C. F. Wilkinson. 1973. Induction of microsomal enzymes in the southern armyworm (Prodenia eridania). *Pestic. Biochem. Physiol.* 3:393-407. [Chem. Abs. 81:33899a, 1974.]
- Brattsten, L. B., and C. F. Wilkinson. 1977. Insecticide solvents: Interference with insecticidal action. *Science* 196:1211-1213.

- Bray, H. G., B. G. Humphris, and W. V. Thorpe. 1949. Metabolism of derivatives of toluene. 3. o-, m-, and p-Xylenes. *Biogeochemistry* 45:241-244.
- Browning, E. 1965. Toxicity and Metabolism of Industrial Solvents. Elsevier, New York. 739 pp.
- Busk, L. 1979. Mutagenic effects of styrene and styrene oxide. *Mutat. Res.* 67:201-208.
- Capellini, A., and L. Alessio. 1971. (English summary) L'eliminazione urinaria di acido ippurico in operai esposti a toluene. [The urinary excretion of hippuric acid in workers exposed to toluene.] *Med. Lav.* 62:196-201.
- Carlsson, A., and T. Lindqvist. 1977. Exposure of animals and humans to toluene. *Scand. J. Work Environ. Health* 3:135-143.
- Chakraborty, J., and J. N. Smith. 1967. Enzymic oxidation of some alkylbenzenes in insects and vertebrates. *Biochem. J.* 102:498-503.
- Ciuchta, H. P., G. M. Savell, and R. C. Spiker, Jr. 1979. The effects of alcohols and toluene upon methylene chloride induced carboxyhemoglobin in rat and monkey. *Toxicol. Appl. Pharmacol.* 49:347-354.
- Claus, D., and N. Walker. 1964. The decomposition of toluene by soil bacteria. *J. Gen. Microbiol.* 36:107-122.
- Clifford, D. R., J. K. Faulkner, J. R. L. Walker, and D. Woodcock. 1969. Metabolism of cinnamic acid by Aspergillus niger. *Biotechnology* 8:549-552.
- Curci, A. 1894. Wirkung und Umbildungen des Mesitylen im Organismus. *Jahresber. Fortschr. Tierchem.* 24:100-101 (Abstract).
- Dagley, S. 1971. Catabolism of aromatic compounds by microorganisms. *Adv. Microb. Phys.* 6:1-46.
- Dagley, S. 1972. Microbial degradation of stable chemical structures: General features of metabolic pathways. Pp. 1-16. *Degradation of Synthetic Organic Molecules in the Biosphere: Natural, Pesticidal, and Various Other Man-made Compounds. Proceedings of a Conference held in San Francisco, Calif., June 12-13, 1971.* National Academy of Sciences, Washington D.C.

- Dagley, S., P. J. Chapman, D. T. Gibson, and J. M. Wood. 1964. Degradation of the benzene nucleus by bacteria. *Nature* 202:775-778.
- Daly, J. 1971. Enzymatic oxidation at carbon. Pp. 285-311 in B. B. Brodie and J. R. Gillette, eds. *Handbook of Experimental Pharmacology. Volume 28, Concepts in Biochemical Pharmacology, Part 2.* Springer-Verlag, New York.
- Davey, J. F., and D. T. Gibson. 1974. Bacterial metabolism of para- and meta-xylene: Oxidation of a methyl substituent. *J. Bacteriol.* 119:923-929.
- Durmishidze, S. V., D. Sh. Ugrehlidze, and A. N. Dzhikiia. 1974. Toluene absorption and transformation by higher plants. *Prikl. Biokhim. Mikrobiol.* 10(2):673-677.
- Dutkiewicz, T., and H. Tyras. 1967. A study of the skin absorption of ethylbenzene in man. *Br. J. Ind. Med.* 24:330-332.
- Dutkiewicz, T., and H. Tyras. 1968a. The quantitative estimation of toluene skin absorption in man. *Int. Arch. Gewerbepathol. Gewerbehyg.* 24:253-257.
- Dutkiewicz, T., and H. Tyras. 1968b. Skin absorption of toluene, styrene, and xylene by man. *Br. J. Ind. Med.* 25:243.
- El Masry, A. M., J. N. Smith, and R. T. Williams. 1956. Studies in detoxication. 69. The metabolism of alkylbenzenes: n-Propylbenzene and n-butylbenzene with further observations on ethylbenzene. *Biochem. J.* 64:50-56.
- Fabre, R., R. Truhaut, and S. Laham. 1960. Recherches sur le métabolisme comparé des xylènes ou diméthylbenzènes. *Arch. Mal Prof. Med. Trav. Secur. Soc.* 21:314-328.
- Feist, C. F., and G. D. Hegeman. 1969. Phenol and benzoate metabolism by Pseudomonas putida: Regulation of tangential pathways. *J. Bacteriol.* 100:869-877.
- Filippi, E. 1914a. Azione fisiologica e comportamento di alcuni derivati del Benzene in confronto con quelli del Cicloesano. *Arch. Farmacol. Sper. Sci. Affini* 18:178-192.
- Filippi, E. 1914b. Azione fisiologica e comportamento di alcuni derivati del Benzene in confronto con quelli del Cicloesano. (Cont. e fine vedi Fasc. prec.) *Arch. Farmacol. Sper. Sci. Affini* 18:193-211.

- Gerarde, H. W. 1960. Toxicology and Biochemistry of Aromatic Hydrocarbons. Elsevier, New York. 329 pp.
- Gibson, D. T. 1971. The microbial oxidation of aromatic hydrocarbons. Crit. Rev. Microbiol. 1:199-223.
- Gibson, D. T., M. Hensley, H. Yoshioka, and T. J. Mabry. 1970. Formation of (+)-cis-2,3-dihydroxy-1-methylcyclohexa-4,6-diene from toluene by Pseudomonas putida. Biochemistry 9: 1626-1630.
- Gibson, D. T., B. Gschwendt, W. K. Yeh, and V. M. Kobal. 1973. Initial reactions in the oxidation of ethylbenzene by Pseudomonas putida. Biochemistry 12(8):1520-1528.
- Gibson, D. T., V. Mahadevan, and J. F. Davey. 1974. Bacterial metabolism of para- and meta-xylene: Oxidation of the aromatic ring. J. Bacteriol. 119:930-936.
- Gillette, J. R. 1959. Side chain oxidation of alkyl substituted ring compounds. I. Enzymatic oxidation of p-nitrotoluene. J. Biol. Chem. 234:139-143.
- Harper, C. 1975. p-Xylene metabolism by rat pulmonary and hepatic microsomes. Fed. Proc. 34:785 (Abstract).
- Harper, C., R. T. Drew, and J. R. Fouts. 1977. Benzene and p-xylene. A comparison of inhalation toxicities and in vitro hydroxylation. Pp. 302-311 in D. J. Jollow, J. J. Kocsis, R. Snyder, and H. V. Edwards, eds. Biological Reactive Intermediates. Proceedings of an International Conference on Active Intermediates: Formation, Toxicity and Inactivation held at the University of Turku, Turku, Finland, July 26-27, 1975. Plenum Press, New York.
- Haugen, D. A., T. A. van der Hoeven, and M. J. Coon. 1974. Purified liver microsomal cytochrome P-450: Separation and characterization of multiple forms. J. Biol. Chem. 250:3567-3570.
- Hayaishi, O. 1966. Crystalline oxygenases of pseudomonads. Bact. Rev. 30:720-731.
- Ikeda, M., and H. Ohtsuji. 1971. Phenobarbital-induced protection against toxicity of toluene and benzene in the rat. Toxicol. Appl. Pharmacol. 20:30-43.
- Jacobsen, O. 1879. Ueber das Verhalten des Cymols im Thierkörper. Ber. Dtsch. Chem. Ges. 12:1512-1518.

- James, M. O., R. L. Smith, R. T. Williams, and M. Reidenberg. 1972. The conjugation of phenylacetic acid in man, sub-human primates and some non-primate species. *Proc. R. Soc. Lond. Ser. B* 182:25-30.
- James, S. P., and D. A. White. 1967. The metabolism of phenethyl bromide, styrene and styrene oxide in the rabbit and rat. *Biochem. J.* 104:914-921.
- Jansen, E. F. 1964. Metabolism of labeled ethylene in the avocado. II. Benzene and toluene from ethylene ^{14}C ; benzene from ethylene ^3H . *J. Biol. Chem.* 239:1664-1667.
- Jansen, E. F., and A. C. Olson. 1969. Metabolism of carbon-14-labeled benzene and toluene in avocado fruit. *Plant Physiol.* 44:786-787.
- Jigami, Y., T. Omori, and Y. Minoda. 1975. The degradation of isopropylbenzene and isobutylbenzene by Pseudomonas sp. *Agric. Biol. Chem.* 39(9):1781-1788.
- Kiese, M., and W. Lenk. 1974. Hydroxyacetophenones: Urinary metabolites of ethylbenzene and acetophenone in the rabbit. *Xenobiotica* 4:337-343.
- Kitagawa, M. 1956. Studies on the oxidation mechanisms of methyl groups. *J. Biochem. (Tokyo)* 43:553-563.
- Kobal, V. M., D. T. Gibson, R. E. Davis, and A. Garza. 1973. X-ray determination of the absolute stereochemistry of the initial oxidation product formed from toluene by Pseudomonas putida 39/D. *J. Am. Chem. Soc.* 95:4420-4421.
- Koga, K., and Y. Ohmiya. 1978. Potentiation of toluene toxicity by hepatic enzyme inhibition in mice. *J. Toxicol. Sci.* 3:25-30.
- Leibman, K. C., and E. Ortiz. 1969. Oxidation of styrene in liver microsomes. *Biochem. Pharmacol.* 18:552-554.
- Leibman, K. C., and E. Ortiz. 1970. Epoxide intermediates in microsomal oxidation of olefins to glycols. *J. Pharmacol. Exp. Ther.* 173:242-246.
- Levin, W., M. Jacobson, E. Sernatinger, and R. Kuntzman. 1973. Breakdown of cytochrome P-450 heme by secobarbital and other alkyl-containing barbiturates. *Drug Metab. Dispos.* 1:275-285.

- Lindqvist, T. 1977. (English summary) The partition coefficient of blood/air and water/air for some common solvents. Arbete Hälso No. 8. National Board of Occupational Safety and Health, Stockholm, Sweden. 15 pp.
- McMahon, R. E. 1971. Enzymatic oxidation and reduction of aldehydes and ketones. Pp. 500-517 in B. B. Brodie and G. Gillette, eds. Handbook of Experimental Pharmacology. Vol. 1. Concepts in Biochemical Pharmacology, Part 2. Springer-Verlag, New York.
- McMahon, R. E., and H. R. Sullivan. 1969. The microsomal hydroxylation of ethylbenzene: Stereochemical, induction and inhibition studies. Pp. 239-247 in J. R. Gillette, A. H. Conney, G. Cosmides, R. W. Estabrook, J. R. Fouts, and G. J. Mannering, eds. Microsomes and Drug Oxidations. Academic Press, New York.
- National Academy of Sciences. 1972. Degradation of Synthetic Chemicals in the Biosphere: Natural, Pesticidal, and Various Other Man-made Compounds. Proceedings of a Conference held in San Francisco, Calif., June 12-13, 1971. National Academy of Sciences, Washington, D.C. 350 pp.
- Nencki, L. von. 1873. Ueber das Verhalten einiger aromatischer Verbindungen im Thierkörper. Arch. Exp. Pathol. Pharmacol. 1:420-425.
- Nomiyama, K., and H. Nomiyama. 1974. Respiratory elimination of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. Int. Arch. Arbeitsmed. 32:85-91.
- Nozaka, J., and M. Kusunose. 1968. Metabolism of hydrocarbons by microorganisms. Part I. Oxidation of p-xylene and toluene by cell-free enzyme preparations of Pseudomonas aeruginosa. Agric. Biol. Chem. 32:1033-1039.
- Ohtsuji, H., and M. Ikeda. 1971. The metabolism of styrene in the rat and the stimulatory effect of phenobarbital. Toxicol. Appl. Pharmacol. 18:321-328.
- Omori, T., and K. Yamada. 1969. Studies on the utilization of hydrocarbons by microorganisms. Part XIII. Oxidation of m-xylene and pseudocumene by Pseudomonas aeruginosa. Agric. Biol. Chem. 33(7):979-985.
- Omori, T., and K. Yamada. 1970a. Studies on the utilization of hydrocarbons by microorganisms. Part XVI. Detection of metabolic intermediates of xylene and pseudocumene. Agric. Biol. Chem. 34(5):659-663.

- Omori, T., and K. Yamada. 1970b. Studies on the utilization of hydrocarbons by microorganisms. Part XVII. Metabolism of p-xylene and related compounds. Agric. Biol. Chem. 34:664-669.
- Omori, T., S. Horiguchi, and K. Yamada. 1967. Studies on the utilization of hydrocarbons by microorganisms. Part X. Screening of aromatic hydrocarbon-assimilating microorganisms and p-toluic acid formation from p-xylene. Agric. Biol. Chem. 31:1337-1342.
- Omori, T., Y. Jigami, and Y. Minoda. 1975. Isolation, identification and substrate assimilation specificity of some aromatic hydrocarbon utilizing bacteria. Agric. Biol. Chem. 39:1775-1779.
- Pagnotto, L. D., and L. M. Lieberman. 1967. Urinary hippuric acid excretion as an index of toluene exposure. Am. Ind. Hyg. Assoc. J. 28:129-134.
- Pang, K. S., and J. R. Gillette. 1978. Complications in the estimation of hepatic blood flow in vivo by pharmacokinetic parameters. The area under the curve after the concomitant intravenous and intraperitoneal (or intraportal) administration of acetaminophen in the rat. Drug Metab. Dispos. 6: 567-576.
- Parkki, M. G., J. Marniemi, and H. Vainio. 1976. Action of styrene and its metabolites styrene oxide and styrene glycol on activities of xenobiotic biotransformation enzymes in rat liver in vivo. Toxicol. Appl. Pharmacol. 38:59-70.
- Patel, J. M., C. Harper, and R. T. Drew. 1978. The biotransformation of p-xylene to a toxic aldehyde. Drug Metab. Dispos. 6: 368-374.
- Patel, J. M., C. R. Wolf, and R. M. Philpot. 1979. Interaction of 4-methylbenzaldehyde with rabbit pulmonary cytochrome P-450 in the intact animal, microsomes, and purified systems. Destructive and protective reactions. Biochem. Pharmacol. 28: 2031-2036.
- Pyykko, K., H. Tahti, and H. Vapaatalo. 1977. Toluene concentrations in various tissues of rats after inhalation and oral administration. Arch. Toxicol. 38:169-176.
- Ramsey, J. C., and J. D. Young. 1978. Pharmacokinetics of inhaled styrene in rats and humans. Scand. J. Work Environ. Health 4(Suppl. 2):84-91.

- Ramsey, J. C., J. D. Young, R. J. Karbowski, M. B. Chenoweth, L. McCarty, and W. H. Braun. 1980. Pharmacokinetics of inhaled styrene in human volunteers. *Tox. Appl. Pharmacol.* 53:54-60.
- Reiner, A. M., and G. D. Hegeman. 1971. Metabolism of benzoic acid by bacteria. Accumulation of (-)-3,5-cyclohexadiene-1,2-diol-1-carboxylic acid by a mutant strain of Alcaligenes eutrophus. *Biochemistry* 10:2530-2536.
- Robinson, D., J. N. Smith, and R. T. Williams. 1955. Studies on the detoxication of 60. The metabolism of alkylbenzenes. Isopropylbenzene (cumene) and derivatives of hydratropic acid. *Biochem. J.* 59:153-159.
- Rogers, J. E., and D. T. Gibson. 1977. Purification and properties of cis-toluene dihydrodiol dehydrogenase from Pseudomonas putida. *J. Bacteriol.* 130:1117-1124.
- Sato, A., T. Nakajima, Y. Fujiwara, and K. Hirose. 1974. Pharmacokinetics of benzene and toluene. *Int. Arch. Arbeitsmed.* 169-182.
- Savolainen, H., and P. Pfaffli. 1978. Accumulation of styrene and neurochemical effects of long-term inhalation exposure. *Scand. J. Work Environ. Health* 4(Suppl. 2):78-83.
- Schachter, D., and J. V. Taggart. 1953. Benzoyl coenzyme A and hippurate synthesis. *J. Biol. Chem.* 203:925-934.
- Schachter, D., and J. V. Taggart. 1954. Glycine N-acylase: Purification and properties. *J. Biol. Chem.* 208:263-275.
- Sedivec, V., and J. Flek. 1976. The absorption, metabolism, and excretion of xylenes in man. *Int. Arch. Occup. Environ. Health* 37:205-217.
- Sherwood, R. J. 1976. Ostwald solubility coefficients of some industrially important substances. *Br. J. Ind. Med.* 33:10-14.
- Sielicki, M., D. D. Focht, and J. P. Martin. 1978. Microbial transformations of styrene and [¹⁴C]styrene in soil and enrichment cultures. *Appl. Environ. Microbiol.* 35(1):124-129.
- Skryabin, G. K., T. F. Solov'eva, L. A. Golovleva, M. Yu. Nefedov, A. M. Zyakun, and I. I. Chervin. 1974. A new product of oxidation of p-xylene. *Dokl. Biochem.* 215:104-105.

Skryabin, G. K., L. A. Golovleva, E. L. Golovlev, A. M. Zyakun, Kh. G. Ganbarov, and Yu. V. Shurukhin. 1978. Anaerobic oxidation of p-xylene by microorganisms. Dokl. Biol. Sci. 236:415-418.

Smith, H. W., N. Finkelstein, L. Aliminosa, B. Crawford, and M. Graber. 1945. The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. J. Clin. Invest. 24:388-404.

Smith, J. N., R. H. Smithies, and R. T. Williams. 1954. Studies in detoxication. 55. The metabolism of alkylbenzenes. (a) Glucuronic acid excretion following the administration of alkylbenzenes. (b) Elimination of toluene in the expired air of rabbits. Biochem. J. 56:317-320.

Snyder, R., and J. J. Kocsis. 1975. Current concepts of chronic benzene toxicity. Crit. Rev. Toxicol. 3:265-288.

U.S. Department of Health, Education, and Welfare. 1973. Criteria for a Recommended Standard... Occupational Exposure to Toluene. HSM-73-11023. U.S. Department of Health, Education, and Welfare. Public Health Service, National Institute for Occupational Safety and Health, Cincinnati, Ohio. 99 pp.

Walker, J. D., and J. J. Clooney. 1975. Effects of poorly metabolized hydrocarbons on substrate oxidation by Cladosporium resinae. J. Appl. Bacteriol. 39:189-195.

Watabe, T., M. Isobe, T. Sawahata, K. Yoshikawa, S. Yamada, and E. Takabatake. 1978. Metabolism and mutagenicity of styrene. Scand. J. Work Environ. Health 4(Suppl. 2):142-155.

Weiner, I. M. 1973. Transport of weak acids and bases. Pp. 521-554 in J. Orloff and R. W. Berliner, eds. Handbook of Physiology, Section 8: Renal Physiology. The American Physiological Society, Washington, D.C.

Williams, R. T. 1959. Detoxication mechanisms. Pp. 194-204, 348-389 in The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds, 2nd edition. John Wiley & Sons, New York.

Withey, J. R. 1978. The toxicology of styrene monomer and its pharmacokinetics and distribution in the rat. Scand. J. Work Environ. Health 4(Suppl. 2):31-40.

Withey, J. R., and P. G. Collins. 1979. The distribution and pharmacokinetics of styrene monomer in rats by the pulmonary route. J. Environ. Pathol. Toxicol. 2:1329-1342.

CHAPTER 6

BIOLOGICAL EFFECTS IN MAMMALS: TOLUENE, THE XYLENES, ETHYLBENZENE, AND CUMENE

This chapter contains reviews of the acute and chronic toxicity of toluene, the xylenes, ethylbenzene, and cumene, their mutagenicity, teratogenicity, and potential for carcinogenicity. Because of the volatile nature of these compounds, special emphasis is placed on neurotoxicity and the "glue sniffing" phenomenon.

Variation in the extent and type of data concerning individual alkyl benzenes, especially those pertaining to acute, subchronic, and chronic toxicity and human health, have made it difficult to present a discussion of each compound or to make comparisons among the alkyl benzenes. Nonetheless, the committee has attempted to summarize the data on the biological activity of the alkyl benzene compounds and to interpret their potential significance to the health of humans.

Current environmental exposure standards for alkyl benzenes such as toluene and xylene are based chiefly upon evidence of their effects on the central nervous system. Because of their high affinity for lipids, these and similar compounds are rapidly taken up by the nervous system. High-level exposures may produce signs and symptoms of dysfunction of the central nervous system within minutes after the beginning of exposure. Of the six compounds being considered in this review, only toluene, xylene, and styrene have received enough attention from investigators to justify reasonably sound conclusions concerning their neurotoxicity. This chapter focuses largely upon the acute and chronic neurotoxic effects of toluene and xylene in mammals. Chapter 7 contains discussions of the effects of styrene and styrene oxide. The organization and writing of these sections were simplified considerably by the existence of excellent recent reviews of the neurotoxicity of toluene (U.S. Environmental Protection Agency, 1979; U.S. National Institute for Occupational Safety and Health, 1973), xylene (U.S. National Institute for Occupational Safety and Health, 1975), and styrene (Harkonen, 1978).

Short-term bioassays are assuming greater importance in the evaluation of genetic properties of a test chemical. The recent suggestion that benzene produces leukemia has stimulated extensive investigations of the clastogenic properties of the aromatic hydrocarbon solvents and limited studies of their ability to induce gene or point mutations. This review presents the limited data that are available concerning the mutagenicity of toluene, xylene, ethylbenzene, and cumene.

There have been very few studies on teratogenicity of benzene and its alkyl derivatives even though these solvents have been included among chemicals suspected of having such an effect (Kuntz, 1976; Yager, 1973).

For convenience, the studies of humans are discussed for each compound under Neurotoxicity and, in the case of toluene, under Deliberate Inhalation of Hydrocarbons as well. A separate section on Clinical Toxicology is included under xylene in order to incorporate data on exposures of small occupational groups. Because studies of populations exposed to alkyl benzenes involve exposure to more than one compound, epidemiological studies for these compounds are discussed in one section, toward the end of this chapter.

In contrast to the majority of biologically active compounds whose toxic effects are typically associated with specific structural characteristics, the toxicity of some compounds appears to be related directly with the overall physical properties of the molecule (e.g., water solubility, vapor pressure, oil/water partition coefficient, etc.). These are the so-called "physical" or structurally nonspecific toxicants, the activities of which appear to result from accumulation in some vitally important part of the cell with lipid characteristics. The alkyl benzenes can be included in this group, which also contains many other volatile, nonionized depressants such as alcohols, ethers, and aliphatic and aromatic hydrocarbons.

In several early toxicological studies with homologous series of compounds of this type, it was observed that toxicity was inversely related to boiling point and that each member of any given series was approximately 3 times more toxic than its lower homologue. The classic studies of Overton (1899) and Meyer (1899) suggested that the toxicity or narcotic action of these compounds reflected their oil/water partition coefficient and depended on the solubility of the compounds in the lipids of the organism. Meyer and Hemmi (1935) concluded that narcosis occurred when the intracellular concentration of the compound in the lipid phase (biophase) reached a critical threshold level. However, Ferguson (1939) noted that the geometric increase in toxicity observed in ascending homologous series of several groups of compounds was similar to the increases in oil/water partition coefficients, decreases in vapor pressure, etc. He concluded that toxicity, like the other properties, represented a heterogeneous phase distribution at equilibrium. Under these equilibrium conditions, the thermodynamic activity in each phase is the same. Ferguson (1939) therefore suggested that compounds acting as structurally nonspecific toxicants showed equal toxicity, not when they attained equal concentrations but when they attained equal thermodynamic activities in the biophase. The thermodynamic activity in the extracellular and intracellular phases is the same at equilibrium and is approximated by the relative saturation of the chemical. Therefore,

measurement of the extracellular concentrations of the material (e.g., the concentration of a gaseous anesthetic in the lung or the concentration of a nonvolatile hypnotic in blood plasma) can provide a measure of its thermodynamic activity in the tissue of the central nervous system. This is important since it provides a predictive capability for assessing the toxicity of many previously untested compounds in the absence of knowledge concerning the nature of the target site or sites. Thus, one can predict that up to the so-called "cut-off" point¹ the toxicity of the alkyl benzenes will increase with increasing number and size of the alkyl constituents in the molecule.

The precise nature of the toxic interactions occurring within the organism remains unknown, but they probably interfere with the structure and function of vital membranes. Since toxicity depends on the maintenance of an equilibrium with the external concentration, the toxic effects are usually completely reversible unless exposure is severe and/or prolonged. Consequently, recovery can be expected to be quite rapid following cessation of moderate exposures. It is possible, however, that with the more highly lipophilic analogues of the alkyl benzenes, which tend to accumulate in the tissues of living organisms, some chronic effects might result from their continuing presence in the organism.

Although this may not be the only mechanism through which alkyl benzenes exert their toxic effects, it is probably largely responsible for their acute neurotoxic (narcotic action) in mammals and for their acute toxicity to such species as fish and insects.

TOLUENE

Acute Exposure to Toluene

Central Nervous System. The primary hazard associated with acute exposure to high levels of toluene and other organic solvents is excessive depression of the central nervous system. This is described in more detail below in the section on neurotoxicity. The acute toxicity of toluene is higher than that for benzene: the 8-hr LC₅₀ in mice was 5,300 ppm (Svirbely *et al.*, 1943), whereas the 8-hr LC₅₀ for benzene was 10,400 ppm. Kojima and Kobayashi (1973) reported that 20,000 ppm toluene was lethal to rats after 30 to 50 min of exposure. Death was attributed to depression of the central nervous system. The average concentrations of toluene in the tissues of the animals that succumbed

¹The "cut-off" point represents the point where in homologous ascending series there is a sudden drop in toxicity.

were as follows: blood, 330 $\mu\text{g/g}$; liver, 700 $\mu\text{g/g}$; and brain, 890 $\mu\text{g/g}$. Wolf et al. (1956) calculated the oral LD_{50} for young adult rats to be 7 g/kg. Carpenter et al. (1976) found the LC_{50} of toluene "concentrate," a mixture of hydrocarbons containing approximately 50% toluene and less than 0.1% benzene, to be 8,800 ppm in rats.

Kimura et al. (1971), who published a similar oral LD_{50} of 6.4 ml/kg for young adult rats, found newborn and 14-day-old rats to be much more susceptible to toluene poisoning than adults. The LD_{50} 's were 1 ml/kg for the newborns and 3 ml/kg for the 14-day-old animals. Kimura et al. (1971) reported that 2 ml/kg was the lowest dose to produce gross signs of poisoning characterized by depression of the central nervous system in young adult rats. They divided this dose level by a safety factor of 1,000 to derive a value of 2 $\mu\text{l/kg}$, which they felt was a reasonable maximum permissible solvent residue limit for single, oral exposures.

A number of episodes of acute overexposure to toluene vapor have been reported. Lurie (1949) and Reisin et al. (1975) published accounts of workers who were rendered unconscious by fumes of the chemical. Longley et al. (1967) related the details of two episodes in which a number of men were quickly affected upon inhalation of an estimated 10,000 to 30,000 ppm toluene. Effects ranged from exhilaration and lightheadedness to dizziness and unconsciousness. Predictably, recovery was quite rapid since the compound is so rapidly mobilized from the brain (Savolainen, 1978) and eliminated from the body. Little clinical evidence of tissue injury was seen in these patients.

Respiratory Tract. Åstrand et al. (1972) demonstrated that exercise can double respiratory uptake of toluene. Anderson and Kaada (1953) reported that toluene has an irritative effect on the respiratory tract and other mucous membranes. In a number of occupational accidents on ships involving estimated short-term exposures to between 10,000 and 30,000 ppm toluene there were no complaints of irritation to eyes, throat, or lungs (Longley et al., 1967).

Eyes. Schmid (1956) observed keratitis in furniture polishers exposed to a mixture of organic solvents. Instillation of solvents into the eyes of cats and ocular exposure of furniture polishers to solvents showed that toluene caused the strongest irritation. This finding was not confirmed by investigators who placed the solvent directly into the eyes of rabbits. In rabbits, only a momentary irritation of the conjunctiva was observed (Wolf et al., 1956). No pathological changes were noted in spray painters exposed to toluene in concentrations up to 1,100 ppm (Greenburg et al., 1942).

Skin. Toluene is a solvent for fats. Its degreasing action, when applied to the skin, may cause contact dermatitis.

Heart. Cardiotoxic effects have been observed in humans and laboratory animals subjected to very highly concentrated vapors of toluene. These effects are discussed below in the section on deliberate inhalation of hydrocarbons. It is unlikely that inhalation or ingestion of low concentrations of toluene would be detrimental to the cardiovascular system. Ogata et al. (1970) did report an apparent decrease in pulse rate in volunteers inhaling 200 ppm toluene, but no significant alteration of blood pressure. No significant effect on heart rate was observed in other persons inhaling 100 to 700 ppm toluene (Åstrand et al., 1972; Gamberale and Hultengren, 1972).

Other Effects. The toxicity of acute exposure to toluene appears to be limited largely to depression of the central nervous system, cardiac arrhythmias, and renal toxicity. Even exposures to quantities of toluene sufficient to produce unconsciousness fail to produce residual organ damage in human victims (Longley et al., 1967; Reisen et al., 1975).

Evaluations of laboratory animals exposed to large doses of toluene also indicate that the chemical is relatively nontoxic. Svirbely et al. (1943) could find no conspicuous pathologic changes in organs of mice exposed to high vapor concentrations of toluene. Bruckner and Peterson (1976) detected only slight, transient rises in serum glutamic-oxaloacetic transaminase (SGOT) activity in mice that inhaled 4,000 ppm toluene for 3 hr. Divencenzo and Krasavage (1974) administered 150, 300, 600, and 1,200 mg/kg toluene to guinea pigs by intraperitoneal injections. Twenty-four hours later they measured serum ornithine-carbonyl transferase (OCT) activity and examined the livers for morphologic change. There was no alteration in OCT activity at any dose level. Only at the highest dosage was there histological evidence of lipid accumulation.

Reynolds and Yee (1968) included toluene in a hepatotoxicity study because of its similarity to hepatotoxic aliphatic halocarbons and lipophilic solvent properties. In contrast to other chemicals tested, administration of a 2.4 g/kg oral dose of toluene had no effect on hepatic glucose-6-phosphatase activity, calcium influx into hepatocytes, or liver morphology in rats after 1, 8, or 24 hr. In a subsequent investigation, Reynolds (1972) observed no effect on a wide battery of hepatotoxicity indices 2 hr after giving 2.4 g/kg of the chemical to rats. These findings suggest that any lipophilic solvation action on hepatocyte membranes by toluene is of little toxicological consequence. Holmberg and Malmfors (1974) provided additional evidence of the nontoxic

nature of toluene by demonstrating in vitro that concentrations as high as 100 µg/ml had no cytotoxic effect on suspensions of ascites tumor cells.

Subchronic Exposure to Toluene

Subchronic exposures to toluene appear to have little toxic potential. In an effort to assess the capacity of toluene to elicit injury under conditions approximating those encountered during glue-sniffing, Bruckner and Peterson (1976) subjected mice and rats 5 times weekly, for 8 weeks, to 3-hr cycles of fresh air alternating with 12,000 ppm concentrations of toluene vapor. Although this exposure was not lethal, it did produce inebriation. A battery of standard toxicologic and histopathologic tests failed to reveal evidence of injury to the lung, liver, or kidney during the 8-week exposure. Jenkins et al. (1970) found that neither continuous exposure to 107 ppm toluene for 90 days nor intermittent (8 hr/day, 5 days/week) exposure to 1,085 ppm for 6 weeks affected body weight gain, hematologic parameters, or the morphology of any number of organs of the rat, guinea pig, dog, or monkey. Similarly, Carpenter et al. (1976) observed no significant alteration of any of a variety of indices of toxicity in rats and dogs exposed via inhalation to 988 ppm of toluene concentrate for 13 weeks. The concentrate consisted of approximately 50% toluene, 15% other benzenes, 14% heptane, 10% cyclohexane, and lesser amounts of other hydrocarbons.

Rhudy et al. (1978) recently reported the results of a 90-day pilot study for a chronic toxicity study of toluene. Male and female rats were exposed by inhalation to 30, 100, 300, or 1,000 ppm of 99.98% pure toluene for 6 hr/day, 5 days/week for 13 weeks. A battery of tests, including hematology, urinalysis, and histopathology, revealed no significant alteration at any exposure level. Appearance, behavior, food consumption, and mortality of the animals were not affected, although there was a slight reduction in body weight gain in males exposed to the high dose.

Tahti et al. (1977) exposed rats to 1,000 ppm toluene vapor 6 hr daily for 1 week. They observed minimal increases in serum glutamic-pyruvic transaminase (SGPT) and SGOT activities, as well as apparent metabolic acidosis. This latter observation is of interest because Taher et al. (1974) reported two cases of metabolic acidosis in humans who had inhaled toluene for its intoxicating effects. They described the condition as renal tubular acidosis because they believed it was due to reversible alteration of the ability of the distal renal tubule to acidify the urine.

Short-term exposure to toluene has relatively little effect on the metabolic capacity of the liver. Fabacher and Hodgson

observed no modifications of liver:body-weight ratio, microsomal protein content, o- and N-demethylation, or various spectral characteristics of cytochrome P-450 in male mice injected intraperitoneally for 3 consecutive days with 100 mg/kg toluene. Other methylated benzenes and a methylated naphthalene increased liver weight and microsomal enzyme activity in the mice, leading the authors to speculate that such compounds were effective inducers because they are lipophilic and persist in the body. Apparently, toluene was ineffective because it was too readily metabolized and excreted.

Ungváry et al. (1976) attempted to design a protocol that would eliminate toluene's rapid turnover rate. They dosed rats daily by intraperitoneal or subcutaneous injection of 0.12 to 1.0 ml/kg analytical grade toluene for 12 days to 4 weeks. Dose-dependent increases were seen in the number and total area of mitochondria per unit of cytoplasmic area in the liver. Similarly, dose-dependent decreases in the average nuclear volume were also observed in hepatocytes of animals receiving intraperitoneal injections. Subcutaneous injection was much less effective in inducing these ultrastructural alterations. The enhanced mitochondrial prominence is interesting in light of a previous report from the same laboratory (Hudák and Ungváry, 1975) of a dose-dependent increase in succinic dehydrogenase activity and a decrease in glycogen content of livers of toluene-treated rats. The toxicological or biological significance of these findings is unclear, although the investigators have suggested that the mitochondrial changes are associated with increased microsomal xenobiotic metabolism. There is evidence that mitochondria, under certain conditions, may be involved in microsomal mixed-function oxidase reactions, possibly serving to transfer reducing equivalents originating from NADPH or NADH through cytochrome b5 to cytochrome P-450 (Schenkman et al., 1973).

Chronic Exposure to Toluene

Blood and Hematopoietic Organs. Although long-term exposure to toluene is quite common in industry, a few reports suggest that it has produced deleterious health effects in workers. One adverse effect that has been tentatively attributed to toluene is myelotoxicity. Until the end of World War II toluene was suspected of having the same hematotoxic effect as benzene. Many of the early studies suggesting this similarity involved the use of toluene contaminated with benzene (U.S. National Institute for Occupational Safety and Health, 1973).

The preponderance of clinical/epidemiological investigations of workers routinely exposed to toluene vapors have failed to reveal any significant abnormalities of the circulating blood and/or bone marrow. Estimated levels of exposure to toluene in these

negative studies were <200-400 ppm (Bänfer, 1961), 80-160 ppm (Capellini and Alessio, 1971), 50-800 ppm (Friborská, 1973), and 60-100 ppm (Matsushita et al., 1975). Comparing toluene-exposed workers and matched controls, Forni et al. (1971) did not find significant difference in the frequency of chromosome aberrations in peripheral blood lymphocytes. In contrast, stable and unstable chromosome aberrations were significantly higher in individuals exposed to benzene.

Greenburg et al. (1942) examined 61 painters who were exposed to solvent mixtures composed largely of toluene. They observed macrocytosis, anemia, and lymphocytosis in some of the workers, no alteration of differential leukocyte counts, reticulocytosis, thrombocytopenia, or leukopenia. Syrovadko (1977) reported that female employees exposed to toluene and other compounds through their work with varnishes exhibited decreased erythrocyte and thrombocyte indices (Syrovadko, 1977). Interpretation of such accounts of toxicity in occupational settings is often complicated by uncertain exposure levels, variable exposure patterns, exposure to multiple chemicals, and/or unrecognized predisposing factors.

Evaluations of the myelotoxicity of toluene in laboratory animals have generally indicated that the chemical is nontoxic. Wolf et al. (1956) have apparently conducted the only long-term toxicity study in which toluene was administered orally. In this study, female rats received 118, 354, or 590 mg/kg toluene 5 times weekly for 6 months. Cell counts of bone marrow and circulating blood revealed no adverse effects. Takeuchi (1969) saw no alterations in peripheral blood counts in rats that inhaled 200, 1,000, and 2,000 ppm of 99.9% pure toluene 8 hr/day for 32 weeks. Rhu et al. (1978) failed to detect any hematologic abnormalities in male and female rats that inhaled 13 weeks to 30, 100, 300, or 1,000 ppm of 99.98% pure toluene 6 hr/day, 5 days/week.

Andrews et al. (1977) investigated the effects of toluene and benzene by measuring the incorporation of ⁵⁹Fe in erythrocytes of mice. They reported that benzene inhibited this incorporation but that toluene did not. In studying the effect of toluene-benzene interactions, they noted that toluene actually protected against inhibition of this process by benzene.

Yushkevich and Malysheva (1975) observed no alteration in erythroblast maturation in the bone marrow of rats subjected 4 times daily for 4 months to a topical application of 10 g/kg toluene. They reported that this rather unusual dosage regimen impaired leukopoiesis, as evidenced by an increase in the number of plasma cells and lymphoid reticular cells in the marrow. Topical application of 1 g/kg of toluene daily did not produce a similar effect.

Horiguchi et al. (1976), however, observed leukocytosis within 10 days in mice that inhaled 1, 10, 100, or 1,000 ppm toluene 6 hr/day. Decreases in circulating erythrocytes were observed in the mice exposed to 100 and 1,000 ppm, whereas thrombocytopenia occurred in the mice exposed to 10, 100, and 1,000 ppm. A slight hypoplastic change was noted in the bone marrow of the group subjected to 1,000 ppm toluene. Dobrokhotov and Enikeev (1977) also observed leukocytosis accompanied by chromosome damage in the bone marrow of rats subjected 4 hr daily for 4 months to 112 ppm of toluene vapor. Benzene also elicited chromosome damage, which was added to that of toluene when the two chemicals were administered together. One month after termination of the exposure, the leukocytosis had disappeared, but the chromosome abnormalities persisted.

The "positive" findings published by Yushkevich and Malysheva (1975), Horiguchi et al. (1976), and Dobrokhotov and Enikeev (1977) should be interpreted with caution since there have been a substantial number of studies of humans and animals in which no evidence of toluene-induced myelotoxicity was seen. It is often difficult to appreciate fully the experimental conditions and protocols used, to interpret the data, and, in the absence of sufficient details about the experimental conditions, to judge the validity or significance of findings in reports that have been translated from foreign languages. For example, the purity of the toluene used in each of the three aforementioned studies was not stated. However, the findings of these investigators should not be entirely dismissed. They may prove to be subtle, heretofore unrecognized hematopoietic responses to toluene.

Several reports link altered immunocompetence to long-term exposure to solvents. Lange and coworkers (1973a) investigated serum complement levels, serum immunoglobulin levels, and leukocyte agglutinins in persons exposed occupationally to benzene, xylene, and toluene. Levels of IgG and IgA (Lange et al., 1973a) and complement (Smolik et al., 1973) were lower in these persons than in controls. Although 10 of 35 solvent-exposed workers had leukocyte agglutinins (Lange et al., 1973b), it was not possible to attribute the effects to any single solvent. Capurro (1976) described changes in gamma globulin fractions and increased prevalence of colds and susceptibility to streptococcal infections in persons who worked at or lived near chemical plants that utilized large quantities of solvents. Bernshtein (1972) did report an inhibitory effect on the phagocytic activity of leukocytes taken from rats exposed via inhalation to 185 ppm toluene 4 hr daily for 6 months. In contrast, Friborská (1973) noted increases in alkaline phosphatase, acid phosphatase, and lactic dehydrogenase activity in leukocytes and/or lymphocytes of workers exposed to

toluene. The authors associated these alterations with increased functional capacity of the cells.

Exposure to solvents has also been tentatively linked with induction of autoimmune disease. A substantial number of patients diagnosed as having glomerulonephritis were found to have had a history of intensive, long-term exposure to solvents (Beirne and Brennan, 1972; Zimmerman et al., 1975). These investigators noted that individual host susceptibility was probably an important factor since so many persons are routinely exposed to solvents without developing the disease.

In these studies and those of Lange and associates, no individual component of the complex solvent mixtures to which the glomerulonephritis patients had been exposed could be singled out as the potential toxicant.

Liver and Kidney. Long-term exposure to toluene appears to have little capacity to injure the liver and most other organs. Greenburg et al. (1942) were the only investigators to suggest an adverse effect of toluene on the liver in an occupational setting. They observed an increased incidence of hepatomegaly in painters exposed from 2 weeks to 5 years to solvent mixtures in which toluene was the major component. Analyses of air samples taken from the work environment revealed exposure levels ranging from 100 to 1,100 ppm toluene.

Capellini and Alessio (1971) observed no changes in liver function in 17 workers exposed for several years to approximately 125 ppm toluene. There has also been a surprisingly low incidence of hepatorenal injury in persons who purposefully inebriate themselves with toluene. For example, Litt et al. (1972) found modest elevations of SGPT levels in only 2% and elevated alkaline phosphatase levels in 5% of a group of 982 glue sniffers. Massengale et al. (1963) and Barman et al. (1964) failed to detect hepatorenal injury in groups of abusers of toluene-based glues. Press and Done (1967) observed slight but transient abnormalities in urinalyses of a small percentage of the glue sniffers they examined and detected no evidence of liver injury. These investigators concluded that any adverse effects would be transient and follow very closely upon intensive exposure. This supposition is supported by Bruckner and Peterson (1976), who demonstrated that intensive inhalation exposure of mice to toluene is followed by small, reversible increases in serum levels of certain cytoplasmic enzymes. Signs of liver (Weisenberger, 1977) and kidney (Kelly, 1975) injury in toluene abusers being treated for behavioral problems cleared spontaneously during hospitalization.

Clinical findings from evaluations of solvent abusers should be interpreted with caution when considering the toxicity of specific

chemicals such as toluene. Patterns and frequency of exposure may differ markedly among individuals. The commercial products favored by many abusers are usually complex mixtures of different compounds. Moreover, the formula for any given product often varies from one manufacturer to another and can be changed at any time. The abuser may use a variety of solvent-containing products, often in combination with alcohol and other drugs. Thus, the stage is set for chemical or drug interactions that may protect the participant or place him at risk. (See next section on Synergism and/or Antagonism.)

Long-term studies with animals have generally revealed little evidence of any residual toxic effect of toluene. Wolf et al. (1956) gave female rats 118, 354, and 590 mg/kg of toluene in olive oil by stomach tube 5 times weekly for 193 days. They observed no adverse effects of growth, mortality, appearance, behavior, organ:body weights, blood urea nitrogen levels, bone marrow counts, peripheral blood counts, or morphology of major organs. These findings indicate that the minimum toxic oral dose of toluene must be greater than 590 mg/kg/day in these animals.

Synergism and/or Antagonism

Sufficient amounts of toluene appear to have the potential to alter significantly the metabolism and resulting bioactivity of certain other chemicals. The time of exposure to toluene relative to the time of exposure to a second chemical could be quite important. Prolonged preexposure to toluene may induce or stimulate mixed-function oxidase activity, thereby enhancing metabolism of the second chemical. Should concurrent exposure occur, toluene, which is readily hydroxylated by the microsomal mixed-function oxidase system, would be expected to inhibit the metabolism of other compounds, which are acted upon by this same system. This phenomenon would be expected to result in a prolonged half-life of both toluene and the other compound. Inhibited metabolism of a second compound may be beneficial or detrimental, depending upon the toxicity of the parent compound versus its metabolite(s). Toluene also undergoes alcoholic oxidation and conjugation reactions subsequent to the initial hydroxylation reaction. Therefore, a substantial dose of toluene could conceivably interfere with the metabolism of compounds that undergo oxidation and glycine conjugation.

Several studies with animals have demonstrated that toluene can significantly influence the biological fate and effects of other agents. Ikeda (1974) demonstrated that 430 mg/kg of toluene, given to rats by intraperitoneal injection in combination with trichloroethylene, reduced the metabolism of the trichloroethylene.

Toluene's metabolism was also diminished. Ikeda et al. (1972) found that simultaneous intraperitoneal administration of toluene and benzene to rats resulted in suppression of the metabolism of both compounds. The mutual suppression was reflected in diminution of urinary excretion of phenol and hippuric acid. Coadministration of toluene and styrene also decreased metabolism. Pretreatment of the rats with phenobarbital decreased the suppressant effects of toluene.

Andrews et al. (1977) coadministered 440 or 880 mg/kg benzene and 1,720 mg/kg toluene intraperitoneally to mice. They observed a marked reduction in urinary excretion of benzene metabolites, coupled with a compensatory increase in pulmonary excretion of unmetabolized benzene. Using liver microsomes in vitro they demonstrated that toluene is a competitive inhibitor of benzene metabolism. When toluene and benzene were administered concomitantly to mice by subcutaneous injection, they determined that toluene did not significantly reduce the total amount of benzene appearing in body tissues, but that it markedly reduced the concentration of benzene metabolites in various tissues including bone marrow. They also found that toluene suppressed the inhibitory effect of benzene on the incorporation of ^{59}Fe into developing erythrocytes, suggesting that toluene may guard against the myelotoxicity of benzene by inhibiting the metabolism of benzene in bone marrow.

Neurotoxicity

Studies of Animals. Numerous studies of high-level exposure to toluene have produced evidence of dysfunction in the central nervous system of animals. Acute lethality appears to result mainly, if not entirely, from depression of the central nervous system (see above). Batchelor (1927) observed a dose-related occurrence of instability, lack of coordination, and mild narcosis in rats exposed daily to toluene vapor at concentrations of 1,600 ppm and 1,250 ppm. No effect was noted at 1,100 ppm. However, since he also reported bone marrow hyperplasia and changes in white and red cell counts, it is likely that benzene was a contaminant. But it is also probable that the observed effects on the central nervous system were caused by toluene since other studies with toluene have yielded similar results. Smyth and Smyth (1928) observed that inhalation exposures of guinea pigs to 1,250 ppm toluene for 4 hr/day for 18 days also resulted in narcosis, whereas longer exposures to 1,000 ppm produced no apparent harmful effects.

Carpenter et al. (1976) reported that rats showed no signs of discomfort resulting from exposure to 1,700 ppm toluene "con-

centrate" for 4 hr, and dogs were unaffected by 760 ppm given for 6 hr. After inhaling 7,800 ppm, cats showed signs of effects on the central nervous system such as tremors, mydriasis, and prostration within 80 min. Rats and dogs inhaling 980 ppm of the toluene mixture showed no ill effects after an exposure of 6 hr/day for 13 weeks. In a similar, more recent study of rats exposed to 99.98% pure toluene vapor at concentrations up to 1,000 ppm for 6 hr/day, 5 days/week for 13 weeks, Rhudy et al. (1978) observed no deleterious effects.

Although most investigators have used inhalation exposures, several have exposed animals via the oral route. Wolf et al. (1956) gave rats oral doses of toluene ranging from 118 to 590 mg/kg body weight 5 times weekly for 193 days. They noted no effects on the growth, behavior, or appearance of the animals. Kimura et al. (1971) estimated that 2 ml/kg body weight is the minimum single oral dose required to produce obvious signs of depression of the central nervous system.

Single exposures of rats to toluene for 4 hr or less have been reported to produce no changes in a conditioned avoidance task at concentrations less than 3,200 ppm and no changes in unconditioned reflexes such as the corneal reflex and the righting reflex below 800 ppm (Krivanek and Mullin, 1978). Similarly, Shigeta et al. (1978) found that single 4-hr exposures to 1,000 ppm concentrations of toluene had little effect on avoidance responses. Although 3,000 ppm did produce changes in response patterns, recovery occurred within an hour after termination of exposure.

Takeuchi and Hisanaga (1977) exposed rats to approximately 1,000, 2,000, or 4,000 ppm toluene for 4 hr. They observed the general behavior of the rats, noted the number of rearings (standing on hind limbs), and recorded the hippocampal and cortical electroencephalogram. At first, rats exposed to 4,000 ppm were more excitable, as evidenced by increased frequency of rearing, but this phase was succeeded by narcosis or depression and an inability to walk. The rats also experienced myoclonic seizures. Exposure to 2,000 ppm resulted in increased rearing throughout the exposure period and occasional myoclonic seizures. Exposure to 1,000 ppm produced no significant increase in rearing nor any apparent depression or seizure activity. Exposure to 4,000 or 2,000 ppm appeared to disturb all phases of sleep, increase the incidence of high frequency electroencephalogram activity, and reduce the frequency of the hippocampal theta wave. Fewer changes were observed in rats exposed to 1,000 ppm. Furnas and Hine (1958) had failed to show any changes in the electroencephalograms of rats exposed to 5,000 ppm for 20 min or 10,000 ppm for 40 min,

although they observed abnormal spike activity after brief exposures to 20,000 ppm.

Ikeda and Miyake (1978) exposed rats to 4,000 ppm of toluene vapor 2 hr daily for 60 days. They examined spontaneous locomotor activity, emotionality, and learning on three different operant schedules. Toluene had no effect on learning or memory of a continuous reinforcement schedule, learning of a fixed-ratio schedule, emotionality, or locomotor activity. However, there was impairment in the learning of a more difficult task, which required the rat to allow at least 12 seconds between responses in order to receive a reward (DRL 12-second schedule). Inferior performance was still observed 80 days after termination of exposure. Histological examination of the brain revealed no changes. The authors suggest that toluene produces diffuse changes in the brain resulting in a subtle deterioration in higher cognitive function.

Mice exposed to 4,000 ppm toluene vapor for 3 hr/day, 5 days a week for 8 weeks were tested with a battery of reflex and behavioral performance tasks (Peterson and Bruckner, 1976). Two weeks after termination of the 8-week exposure, the animals exposed to toluene had better test scores than did the control animals, demonstrating, according to these authors, the development of tolerance to toluene.

Although almost all studies of toluene toxicity, whether chronic or acute, have demonstrated only minimal effects at concentrations of 1,000 ppm or less, several reports indicate the possibility of changed function of the central nervous system at lower levels. For instance, Battig and Grandjean (1964) exposed rats to toluene 4 hr/day for 3 weeks and then measured both acquisition and extinction of a conditioned avoidance response. The concentration of toluene varied from 550 to 800 ppm. No effect on acquisition of the avoidance behavior occurred, but extinction of the response was somewhat slower. In another study, exposure of rats to 150 ppm toluene for 0.5, 1, 2, and 4 hr had minimal effects on performance of a multiple fixed-ratio, fixed-interval operant task. The 0.5-, 1-, and 2-hr exposures resulted in higher response rates in rats on the fixed-interval schedule, but the 4-hr exposure produced no significant changes (Geller et al., 1978).

Perhaps the lowest level of toluene reported to have any effect on behavior is 1 ppm. This level as well as concentrations of 1 and 1,000 ppm were found by Horiguchi and Inoue (1977) to depress spontaneous locomotor activity in mice exposed for 6 hr/day for 20 days. Their data indicate similar effects on motor activity among the exposure groups. Earlier, Gusev (1972) reported changes in muscle

response latencies (motor chronaxies) in rats exposed continuously to 4 ppm toluene for 85 days. The validity of the results of these two studies is questionable in view of the lack of effects observed at much higher levels of exposure to toluene in other experiments.

In summary, studies with animals have yielded only minimal evidence that acute or chronic exposures to toluene produce effects on the central nervous system at atmospheric concentrations below 1,000 ppm.

Studies with Humans. Exposures of humans to toluene may be grouped into three categories: occupational exposures, deliberate inhalation of toluene or toluene-containing substances, often referred to as "glue sniffing," and experimental studies. Occupational exposures and glue sniffing more often than not involve complex mixtures of solvents. This complicates the interpretation of data from studies of such exposures.

Occupational Exposures. Wilson (1943) evaluated the effects of toluene on 100 workers who were exposed occupationally for 6 to 8 hr daily for 1 to 3 weeks. Concentrations of toluene between 500 and 1,500 ppm produced increases in reaction time, loss of coordination, and a variety of subjective symptoms such as dizziness, weakness, headache, and nausea. Exposure to concentrations ranging from 200 to 500 ppm was associated with slight impairments in reaction time, coordination, and memory along with similar, though less pronounced, subjective complaints reported at higher concentrations. At concentrations between 50 and 200 ppm, only mild subjective symptoms such as loss of appetite and lassitude were reported.

Longley et al. (1967) described two episodes of acute exposure to toluene involving 36 men. In one incident concentrations were estimated to have ranged from 10,000 ppm at waist level to 30,000 ppm at floor level. The effects of these concentrations for unspecified exposure periods were dizziness, "drunkenness," collapse, and loss of consciousness. Recovery was quite rapid, and there were no residual after-effects.

Parmeggiani and Sassi (1954) studied 11 workers in the paint and pharmaceutical industry who were exposed to toluene vapor concentrations ranging from 200 to 800 ppm. Irritation of the conjunctiva and of the upper respiratory tract mucosa was found in one worker, and nervous excitability in six others. Similarly, Capellini and Alessio (1971) described symptoms of stupor, nervousness, and insomnia, indicating effects on the central nervous system, in one worker who had been exposed to concentrations of toluene ranging from 210 to 300 ppm for several years. Seventeen

other workers, who had been exposed to concentrations of toluene ranging from 80 to 160 ppm were unaffected. Matsushita et al. (1975) reported abnormal tendon reflexes, reduced grasping power, and decreased finger agility in 38 female shoemakers who had been exposed chronically to a mixture of solvents containing 60 ppm toluene, but the exposure concentration was uncertain.

Lindstrom (1973) gave psychological tests to 168 workers who had been exposed to hydrocarbon solvents for periods ranging from 1 month to 30 years (mean, 6 years). Fifty-one of the workers had been exposed primarily to toluene or a combination of toluene and xylene. Sensorimotor speed, psychomotor performance, and visual accuracy of the solvent-exposed workers were inferior to performances of control subjects.

In a similar study, Hänninen et al. (1976) examined behavioral effects in 100 car painters who had been exposed chronically to hydrocarbon solvents. Although the exposures involved several different solvents, toluene was present in the greatest amount (30.6 ppm, which is 30.6% of the TLV for toluene). The authors estimated that the workers had been exposed to only 32% of the combined TLV's for the organic solvents in the solvent. The psychological tests revealed impairment of visual intelligence, verbal memory, verbal intelligence, and attention in emotional reactivity as compared with a carefully matched control group. No differences were noted in reaction time or motor performance. Other studies of these same subjects demonstrated no significant increase in abnormalities of electroencephalogram, although there were slight increases in peripheral sensory and motor nerve conduction velocities (Seppäläinen et al., 1978). An epidemiological study of workers exposed chronically to hydrocarbon solvents indicated an increased incidence of non-specific neuropsychiatric disorders such as nervousness, irritability, insomnia, and impairments of memory and reasoning (Axelson et al., 1976).

Experimental Studies. von Oettingen et al. (1942a,b) exposed three human subjects to several different concentrations of toluene for 8 hr daily, twice weekly, for 3 months. They observed no definite effects at concentrations of 50 and 100 ppm, but 200 ppm produced paresthesia of the skin, confusion, muscular weakness, impaired coordination, headache, nausea, dilation of the pupils. After termination of exposure, subjects experienced fatigue, confusion, insomnia, and restlessness. Such effects increased in severity with increases in toluene concentration until, at 800 ppm, the subjects experienced severe fatigue, nausea, mental confusion, staggering gait, and lack of self-control with after-effects, which included insomnia lasting

for several days. Carpenter et al. (1944) reported mild throat and eye irritation and slight exhilaration in two subjects exposed to 220 ppm toluene for 7 hr. As in the study by von Oettingen et al. (1942a,b), the signs and symptoms increased in number and severity as the toluene concentration was increased.

Gamberale and Hultengren (1972) exposed human subjects to 100, 300, 500, or 700 ppm toluene for 20-minute periods and measured their performance on tests of simple and choice reaction time. Simple reaction time was not significantly affected at 100 ppm, but was slowed at 300 ppm. Choice reaction time was unaffected at concentrations below 700 ppm, which led the authors to suggest that complex functions of the central nervous system are less affected by toluene than are simpler functions. The opposite conclusion was reached by Hänninen et al. (1976) and Lindstrom (1973) in their studies of workers exposed to toluene. However, Ogata et al. (1970) also reported that the reaction time was increased in subjects exposed to 200 ppm toluene for 3 or 7 hr, whereas they observed no change at 100 ppm. Since they also found decreases in systolic blood pressure and pulse rate at 200 ppm, they considered this an unacceptable level of exposure.

Gusev (1968) examined the effects of inhaled toluene vapor on the electroencephalograms of human subjects. Toluene concentrations of 1 mg/m³ were reported to cause significant changes in the electroencephalogram from the left temporal-occipital leads in four subjects. The concentration of toluene said to have effects on the electroencephalograms was even lower than the odor threshold determined in the same experiment. No other study has reported any effect on the central nervous system at such low levels as toluene. Therefore, the results must be viewed with considerable skepticism.

Deliberate Inhalation of Hydrocarbons (Glue Sniffing)

Intoxication induced by the deliberate inhalation of hydrocarbon solvents is not uncommon among adolescents. This phenomenon is often called "glue sniffing" since model airplane glue has often been used. Paint thinners, cleaning solutions, gasoline, aerosol propellants, and other substances containing a high proportion of volatile hydrocarbons have also been deliberately inhaled by teenagers and older individuals, including those with access to such compounds at work. Common to all of these substances is the ability to produce acute changes in the central nervous system, which are perceived as a "high." The intoxicating substance usually contains a mixture, often poorly defined, of hydrocarbon compounds, including alkyl benzenes. Toluene is the alkyl benzene most frequently implicated as the cause of adverse effects associated with

acute or repetitive deliberate inhalation. This subject has been reviewed by Hayden et al. (1977), Barnes (1979), Watson (1977), Lewis and Patterson (1974), and Wyse (1973).

Lethal Effects of Glue Sniffing. Sudden death due to solvent sniffing has been reported in a number of countries (Alha et al., 1973; Bloch and Tadjer, 1975; Hayden et al., 1977). Many of these cases appear to have been due to a fatal anesthetic effect. For example, four young adolescents were found dead in an automobile following an estimated exposure to 2,050 ppm toluene (Nomiyama and Nomiyama, 1978). Cardiac arrhythmia has been suggested as a cause of sudden death following deliberate inhalation of volatile hydrocarbons, particularly freon aerosol propellants and other halogenated hydrocarbons. Traumatic deaths during the intoxicated state are also not uncommon.

Bass (1970) noted that exercise or stress had frequently preceded death due to sniffing, perhaps reflecting an adrenergic effect associated with a cardiac arrhythmia or the excitement of light plane anesthesia. He suggested that hydrocarbon solvents produce cardiac arrhythmias, particularly ventricular fibrillation, by sensitizing the heart to adrenergic stimuli. Chenoweth (1946) reported that inhalation of various hydrocarbons, including toluene and xylene, potentiated epinephrine-induced ventricular fibrillation in dogs.

Taylor and Harris (1970) described electrocardiographic changes in mice inhaling toluene-containing model airplane glues for 10 minutes. Alterations, including slowing of the heart rate and a slight prolongation of the P-R interval in the electrocardiogram, persisted for at least 30 minutes. These effects were exacerbated when the mice were made to be anoxic beginning 3 minutes following cessation of glue inhalation. Furthermore, asphyxia plus glue sniffing resulted in second degree atrioventricular block, a clinically significant cardiac arrhythmia, in all 12 mice tested. Similar effects were observed when toluene was substituted for the glue. The effects suggest a direct action of toluene on the sinoatrial node and on atrioventricular conduction in mice. Electrocardiograms of rats inhaling toluene have revealed adverse effects such as disorders of repolarization and arrhythmias (Bereznyi et al., 1975; Morvai et al., 1976).

Nonlethal Effects of Glue Sniffing. Clearly, the effects of toluene on the central nervous system are crucial both to the euphoria produced by deliberate inhalation and to its acute toxicity, including sudden death. Deliberate inhalation of toluene-containing solvent mixtures may also affect other organ systems or may lead to chronic toxicity of the central nervous system. In many cases, particularly those described in the early literature,

ciency. In the absence of additional case reports, animal studies may be required to determine whether hyperactive bone marrow is sensitive to toluene. The literature on deliberate solvent inhalation thus provides no incontrovertible evidence that toluene produces hematological effects. This is in keeping with similar negative hematological findings in the more recent animal toxicological and occupational health studies described earlier in this chapter.

Renal and Metabolic Effects of Glue Sniffing. Several investigators have reported that deliberate inhalation of toluene produces metabolic acidosis (Fischman and Oster, 1979; Moss et al., 1980; Taher et al., 1974). Taher et al. (1974) ascribed two cases to a defect in distal renal tubular acidification. One patient had flaccid paralysis and a history of episodic, generalized muscle weakness following 4 to 7 days of sniffing what was reputed to be toluene. He was found to have a hypokalemic, hyperchloremic acidosis and an inappropriately high urinary pH. The patient responded to treatment with potassium chloride. After subsequent similar episodes following sniffing, he was hospitalized for more intensive evaluation. At that time, toluene was detectable in the patient's blood. Renal potassium wastage was documented by the discovery of significant urinary loss of potassium despite low serum and total body potassium levels. Proximal renal tubular function was normal. Further evaluation after the patient had abstained from toluene revealed completely normal renal function. A second patient, who had been sniffing an aerosol paint containing 60% toluene (other contents not stated), exhibited nausea on two occasions and had a hyperchloremic acidosis. Toluene was detectable in the serum. The authors concluded that renal tubular acidosis might be a life-threatening complication of toluene abuse.

More recently, Fischman and Oster (1979) reported three patients with a history of recurrent toluene abuse who were hospitalized with severe metabolic acidosis. All three had been sniffing transmission fluid, which was described as containing 10% toluene. Of note were specific electrolyte abnormalities, which authors tentatively ascribed to the presence of the metabolic products of toluene--hippuric acid and benzoic acid. Two of the three patients were hypokalemic, a somewhat unusual finding in acidosis with a high anion gap. Both hypokalemic patients were described as having muscular weakness, and one of the patients died following further toluene-sniffing episode. Based on clinical laboratory findings, distal renal tubular acidosis was believed to be present in two of the three patients.

These two studies strongly support the possibility that inhalation of high concentrations of toluene produces metabolic alterations. At least some of the alterations in pH and electro-

lytes appear to have been due to an effect on the function of distal renal tubules, which might have been caused by toluene or its metabolites in the urine. The suggestion that acid metabolites of toluene (e.g., benzoic and hippuric acids) are responsible for the observed electrolyte abnormalities requires confirmation.

Each of the five subjects with acidosis had a history of multiple toluene abuse, raising the possibility that the effect is either not due to a single dose or may be conditioned by changes in the metabolism of toluene induced by previous exposure. Some clinical manifestations of the reported metabolic alterations may mimic those usually attributed to the effects of toluene on the central nervous system. In particular, hypokalemia often produces significant muscular weakness including flaccid paralysis. It is conceivable that altered pH and electrolytes may be more commonly responsible for the manifestations of toluene abuse than is usually recognized. Hypokalemia may also be important in that it potentiates cardiac arrhythmias, particularly those caused by other agents. Accordingly, toluene-induced hypokalemia may contribute to the arrhythmic effects of other components in solvent mixture.

Moss et al. (1980) have provided a detailed description of the clinical findings and course of a 27-year-old female with a reversible Fanconi's syndrome and distal renal tubular acidosis. The patient, who was hospitalized because of profound weakness, had a 9-month history of glue inhalation. The authors also briefly noted four other individuals with histories of glue or paint sniffing who had hyperchloremic metabolic acidosis with low blood bicarbonate levels. Unfortunately, they did not specify the contents of the glue or paint in any of these cases. In an interview study of adults, Zimmerman et al. (1975) associated renal glomerular disease with a history of solvent exposure. But again, it is difficult to determine which hydrocarbons might have been responsible for such effects.

A case of hepatorenal syndrome was attributed to toluene by O'Brien et al. (1971). This patient was a 19 year-old who had a 3-year history of sniffing, most recently sniffing of a cleaning fluid that contained 80% toluene as well as a number of unidentified components. Serum toluene was estimated to be 160 mg/liter. An odor of the solvent in the breath was still detectable 36 hr after admission. Renal insufficiency required peritoneal dialysis. Evidence of renal damage included hematuria and proteinuria. Subconjunctival hemorrhages and a prolonged prothrombin time were presumably secondary to the liver disease. Complete recovery apparently occurred. The hepatic and renal effects of halogenated hydrocarbons, particularly carbon tetrachloride, are well-known.

As there is no other evidence of toluene-induced hepatorenal syndrome in animals or humans, it is questionable whether the case reported by O'Brien et al. (1971) is due to toluene rather than to an unidentified halogenated hydrocarbon component of the mixture.

Neurological Effects. Grabski (1961) reported the case of a 21-year-old man who had inhaled toluene regularly for 2 years. A neurological examination of this subject was normal in most respects, but there were signs attributable to cerebellar dysfunction, including disorders of gait, intention tremor of hands and feet, and adiadochokinesis. After 8 more years of toluene abuse, the same patient was examined by Knox and Nelson (1966) who observed ataxia, tremor, lack of coordinated movement, Babinski's sign, and emotional lability. A generally slower electroencephalogram and an abnormal pneumoencephalogram suggested the presence of diffuse cerebral atrophy.

Other case reports support the conclusion that excessive inhalation of toluene leads to diffuse disorders of cerebellar and other cerebral functions and that the disorders vary in degree with the intensity and duration of exposure (Boor and Hurtig, 1977; Kelly, 1975; Sasa et al., 1978; Satran and Dodson, 1963). Prolonged abuse may lead to permanent encephalopathy (Knox and Nelson, 1966; Sasa et al., 1978), whereas the effects of shorter or lower level exposures appear to be completely or partially reversible (Boor and Hurtig, 1977; Keane, 1978).

Although Gota et al. (1974) suggested that toluene may produce peripheral neuropathy as well as effects on the central nervous system, there is little evidence to support this unless the toluene was contaminated with other substances such as n-hexane. For example, the patient of Boor and Hurtig (1977), who experienced cerebellar dysfunction upon intensive inhalation of 99% pure toluene, exhibited no sensory or neuromuscular involvement. However, other investigators have suggested that toluene may influence the neurotoxic potential of n-hexane (Suzuki et al., 1974) or even damage peripheral nerves (Goto et al., 1974) since a number of persons have developed peripheral neuropathies upon sniffing mixtures of toluene and n-hexane. These neuropathies can apparently be either sensory or sensorimotor, with or without amyotrophy (Shirabe et al., 1974). In the majority of reported cases involving hexane-toluene mixtures, the victims had abused products containing large amounts of toluene but no n-hexane for years without apparent difficulty (Korobkin et al., 1975; Shirabe et al., 1974; Towfighi et al., 1976). Only a few weeks to months after switching to products containing n-hexane, the victims experienced progressive weakness and numbness of the extremities. A search of the literature yielded no reports attributing peripheral neuropathy to the inhalation of toluene alone.

The possible contribution of toluene to n-hexane neurotoxic potential is minimized by findings of Suzuki et al. (1974). These investigators administered 910 mg/kg of n-hexane alone, and in combination with 1.18 g/kg of toluene, by intraperitoneal injection to rats. The toluene had no effect on the rate of elimination of n-hexane from the blood, nor did n-hexane influence urinary excretion of toluene's major metabolite, hippuric acid. They suggested that the two compounds do not influence one another because each is metabolized by a different enzyme system. Apparently, no one has determined experimentally whether toluene can influence the time of onset and/or the magnitude of n-hexane-induced neuropathy.

Summary

Acute or chronic exposure of animals and humans to very high levels of toluene (>750 ppm) can produce dysfunction of or even permanent damage to the central nervous system. Except under conditions of excessive exposure, such as that experienced by glue sniffers, the effects of toluene appear to be mild and readily reversible. Studies of humans exposed either occupationally or experimentally to toluene are in fair agreement that concentrations of 200 ppm or greater have undesirable effects, whereas psychological tests of workers have indicated the possibility of slight, subtle changes in function of the central nervous system at concentrations as low as 30 ppm. Since even this value is high by ambient standards, it seems safe to conclude that current or projected environmental levels of toluene alone should not be harmful to the nervous system.

Intentional inhalation of hydrocarbons by humans can be interpreted as a type of "maximum tolerated dose" experiment for studying toxicity in animals. Effects on the central nervous system occurring acutely and repetitively in these individuals are, in essence, an approximation of those resulting from the highest possible sublethal concentrations. As such, any effects other than those on the central nervous system observed in chronic inhalation abusers can be regarded as the maximum toxicity to be expected under conditions of repetitive, acute inhalation for perhaps a decade or longer. Reasonably good, but still incomplete, evidence indicates that the nonneurological toxicity of toluene appears to be restricted to the kidneys. Hematological toxicity in individuals with preexisting hemolysis is also possible but requires confirmation. Obviously, literature on the abuse of hydrocarbons cannot provide information concerning the effects of many decades of toluene inhalation, nor is it pertinent to all of the many possible combinations of toluene with other agents. However, on balance, it strongly suggests that

acute or repetitive inhalation of toluene at levels below those causing effects in the central nervous system is without apparent significant health risk.

XYLENE

Acute Exposure to Xylene

Cameron et al. (1938) compared the toxicity of various methylated benzene derivatives, including o-, m-, and p-xylene in a number of laboratory animal strains. The xylenes were found to be somewhat more toxic than toluene and more toxic than mesitylene, pseudocumene, and heavy naphtha fractions. In rats and mice the lethal dose for subcutaneous injection was 5-10 ml/kg body weight for p- and m-xylene and 2.5-5.0 ml/kg body weight for o-xylene. The lethal dose for intraperitoneal injection was 2-2.5 ml/kg body weight for p- and m-xylene and 1.5-2 ml/kg body weight for o-xylene.

Wolf et al. (1956) reported that the acute LD₅₀ for male mice receiving a single peroral administration of 95% pure xylene (ortho, 52% meta, 24% para) was 4.3 g/kg. Repeated skin contact with the same solution led to moderate to marked erythema and slight necrosis in rabbits. Instillation of the mixture into rabbit eye led to conjunctival irritation and very slight, transient corneal injury. Cutaneous inflammatory effects of xylene have also been studied by Rigdon (1949) and Falck and Möller (1963).

Inhalation studies by Cameron et al. (1938) revealed similar toxicity for o- and m-xylene: concentrations of 2,000-3,000 ppm for 24 hr resulted in fatalities, and the mice were reportedly more sensitive than rats to m-xylene. p-Xylene appeared to be less toxic in that deaths were not observed in either rats or mice that had been exposed to 4,912 ppm for 24-28 hr. Fatality did occur after the animals had been exposed to 19,650 ppm for 12 hr. Exposure of rats for 8 hr daily for 14 days to 1,000-1,500 ppm of the various xylenes produced no fatalities. No specific organ changes were observed on autopsy. Studies in rabbits showed no evidence of any overt hematological effects following subcutaneous injection. The source and purity of the compounds used were not specified. In general, only small groups of animals were studied in this relatively early report.

Carpenter et al. (1975) studied the inhalation toxicology of a mixture of xylenes in several species. Using gas chromatography they determined that the xylene mixture contained 65.0% m-xylene, 7.8% p-xylene, 7.6% o-xylene, 19.3% ethylbenzene, and trace amounts of toluene.

of other compounds, not including benzene. The LC_{50} for male rats after a 4-hr inhalation exposure was 29 (22-37) mg/liter. Pathological findings in the 16 rats that died after exposure to 43 mg/liter included two cases each of atelectasis, hemorrhage, and interlobular edema of the lung. At concentrations as low as 5.8 mg/liter, the investigators observed transient irritation, protraction of the eyes, and lack of coordination in the extremities. No effects were apparent at 2.5 mg/liter. Osmotic fragility of the red cells of rats was apparently unchanged after a 45-minute exposure to a lethal level of mixed xylenes. Four male cats died after inhaling 41 mg/liter for 2 hr. They exhibited a classic nervous system effect: the sequential development of salivation, ataxia, tonic and clonic spasms, and anesthesia followed by death. Pathological examination revealed no lesions that were obviously related to the exposure. Respiratory tract irritation, as evidenced by depressed respiratory rate (50% or more), was observed in mice exposed to 5.6 mg/liter or more for 1 minute. This did not occur at 2.0 mg/liter or during the 15-minute period after exposure. Dogs exposed to approximately 4 mg/liter experienced increased lacrimation that began after 1 hr and persisted throughout the 4-hr exposure period. Rats exposed to the same concentration displayed a slight loss of coordination by the second hour of exposure. No unusual effects were observed at exposures to approximately 2 mg/liter.

Bonnet et al. (1979) determined the LC_{50} for mice exposed for 6 hr to 97%-98% pure solutions of the three xylene isomers. Observed LC_{50} levels were 5,267 ppm for m-xylene, 4,595 ppm for o-xylene, and 3,907 ppm for p-xylene. Other LC_{50} levels included benzene, 14,122 ppm; toluene, 6,942 ppm; and styrene, 2,429 ppm.

Subchronic Exposure to Xylene

Carpenter et al. (1975) also conducted studies of subchronic exposures to xylene. They exposed 4 male beagles and 25 male rats to 3.5 mg/liter, 2.0 mg/liter, 0.77 mg/liter, or to control air 6 hr daily, 5 days weekly for up to 66 days. Rats were sacrificed for study at 15 days, 35 days, and at the end of the exposure period. The beagles were sacrificed at the end of the study. The investigators observed no evidence of toxicity of xylene. Hematological tests, blood chemistries, including liver function tests, urinalyses, pathological examination, and body weights, revealed no differences between the control and exposed animals. Following these subchronic exposure regimens, rats were as susceptible to acute lethal exposure as the previously unexposed rats had been, suggesting that no protective adaptive mechanism had developed.

Chronic Exposure to Xylene

Jenkins et al. (1970) evaluated the relatively long-term inhalation toxicology of o-xylenes in rats, guinea pigs, monkeys, and dogs. Animals of each species were exposed to either 780 ppm for 8 hr daily, 5 days weekly for 30 exposures or to 78 ppm continuously for 90 days. Mortality during the repetitive exposure experiment was 3/15 rats, 0/15 guinea pigs, 0/2 dogs, and 1/3 monkeys. One of the dogs was tremulous. Only one rat died during the continuous exposure experiment. Hematological studies and evaluation of necropsy material did not show any effect of o-xylene.

Xylene-induced liver injury was suggested in a study in which male guinea pigs were injected intraperitoneally with 1,000 mg/kg American Chemical Society reagent grade xylene (isomer not specified) (Divincenzo and Krasavage, 1974). The investigators observed an increase in serum ornithine carbamyl transferase, which is said to be an indicator of hepatocellular damage. Histological examination revealed a moderate degree of hepatic lipid accumulation but no tissue necrosis. After intraperitoneal injections of 2,000 mg/kg, three of four guinea pigs died. Toluene injections of 1,200 mg/kg produced far less severe hepatic effects than did xylene.

NEUROTOXICITY

Studies of Animals

The current occupational exposure standard for xylene, like toluene, is based primarily upon its effects on the central nervous system (U.S. National Institute for Occupational Safety and Health, 1975).

Carpenter et al. (1975) reported that rats exposed to mixed xylenes for 4 hr at a concentration of 2,970 ppm showed signs of irritation and prostration within 2 to 3 hr. At concentrations of 1,340 ppm, poor coordination was observed after a 2-hr exposure. Both dogs and rats showed no obvious signs of distress when exposed to 580 ppm for 4 hr. These data are in good agreement with the early experiments of Batchelor (1927), in which the exposure to 1,600 ppm xylene (of undetermined purity) for 18-20 hr/day resulted in the death of two of four rats within 2 days, whereas rats exposed to 980 and 620 ppm for 7 days showed no obvious signs of involvement of the central nervous system. In the experiments by Carpenter et al. (1975), rats and dogs were not affected adversely by exposures to 180, 460, or 810 ppm xylene for 6 hr daily, 5 days per week for 13 weeks. The

concentration at which Carpenter et al. (1975) observed narcotic effects in rats was also similar to those reported by Lazarew (1929) for mice.

Jenkins et al. (1970) observed no histological effects on the brains and spinal cords of monkeys and dogs exposed to 220 ppm o-xylene for 8 hr/day, 5 days/week for 30 days or to 78 ppm continuously for 90 days.

Battig and Grandjean (1964) examined the effects on avoidance conditioning in rats exposed to xylene vapor at a mean concentration of 600 ppm (550-800 ppm). Exposures lasted 4 hr/day for 3 weeks. Xylene had no definite effects on any phase of avoidance testing although the xylene-exposed animals had a slightly higher percentage of correct avoidance responses during the second week of exposure and a slightly slower rate of extinction of the avoidance response during the third week of exposure.

Dési et al. (1967) investigated the ability of rats to learn mazes after they had been given daily subcutaneous doses of xylene (0.5 ml/100 g body weight) for 6 weeks. The exposed rats ran the maze much more slowly than controls, and their running times declined at a significantly slower rate. In the same experiment, the investigators measured the running times of rats that had learned the maze prior to injections of xylene for 28 days in daily doses of 0.02, 0.05, or 0.10 ml/100 g body weight. Ataxia and death of some animals occurred at the 0.10 ml/100 g dose. Although the running times for the groups receiving xylene were longer, the differences were not statistically significant. The authors concluded that xylene interfered with the ability to learn a maze more than it did with the ability to perform trained behavior. However, highly significant weight losses occurred in the rats given injections of 0.5 ml/100 g body weight, which surely confounds attempts to draw any conclusion concerning the effects of xylene on cognitive function.

Savolainen et al. (1979a) studied behavioral and neurochemical effects in 2-month-old male Wistar rats exposed to 300 ppm of xylene vapor for 6 hr/day, 5 days/week with or without simultaneous ingestion of ethanol for 5 to 18 weeks. Xylene inhalation alone increased microsomal superoxide dismutase activity in the brain after 14 weeks of exposure. Inhalation of xylene plus ingestion of ethanol caused increased proteolysis after 9 and 14 weeks of exposure, but cerebral superoxide dismutase failed to effect an increase. Preening frequency decreased transiently after 6 and 9 weeks in the groups exposed to ethanol and xylene and after 12 weeks in the group exposed to xylene alone. Increased ambulation occurred only in the group receiving xylene plus ethanol after 12 and 14 weeks of

exposure. These observations suggest that there may be important interactions between solvents, such as xylene with alcohol, although their significance and the biochemical mechanisms of action are unclear.

Gusev (1972) reported that rats exposed for 85 days to xylene in a concentration of 15 mg/m³ experienced changes in function of the central nervous system. The results of histological examination were virtually identical to those reported for toluene. For neither toluene nor xylene is it possible to place much weight on the data since methods and results are not described clearly. Moreover, apparently, the experimental findings have not been repeated by other workers.

Human Studies. Although early accounts of the effects of xylene on humans contained evidence of dysfunction of the central nervous system, the solvents usually contained appreciable quantities of benzene and other hydrocarbons (Stocké, 1929). For our purpose, only those studies involving exposure primarily to xylene, with little or no benzene contamination, will be considered.

Experimental Exposure. Nelson *et al.* (1943) exposed men and women to vapors of xylene and other solvents for 3 to 5 minutes. A majority of the subjects reported that a concentration of 200 ppm causes irritation of the eyes, nose, and throat. These investigators estimated that 100 ppm was safe for an 8-hr working day.

Carpenter *et al.* (1975) exposed groups of volunteers between 21 and 49 years old to various concentrations of a mixture of xylene isomers (65.0% *m*-xylene, 7.8% *p*-xylene, 7.6% *o*-xylene, 19.3% ethylbenzene, and traces of other compounds). During two series of 10-second inhalations, all six volunteers detected the odor of xylene at 14 ppm, none detected it at 0.14 ppm, and 1.4 ppm was detected 67% of the time. The authors concluded that a likely odor threshold was 1.0 ppm (0.0045 mg/liter). In a separate study, six individuals between 21 and 60 years old inhaled 110, 230, 460, and 690 ppm xylenes for 15 minutes each. At the highest concentration, four of six exposed subjects experienced dizziness and eye irritation, two reported throat irritation and tearing, and three stated that they tasted something. All of these effects were gone within 1 hr following exposure. At 460 ppm, four subjects again reported eye irritation, and there was one complaint of throat irritation, one of tearing, and one of dizziness. At 230 ppm, dizziness, tearing, and eye irritation were reported by one subject. During exposure to 110 ppm (0.46 mg/liter), the only symptom was mild throat irritation, which was reported by only one volunteer. However, that individual did not report this symptom at a higher concentration. The authors concluded that concentrations of 110 ppm or less should not be objectionable to most people.

Gamberale et al. (1978) examined the effects of exposure to a mixture of xylenes (79%) and ethylbenzene (21%) on tests of numerical ability, reaction time, short-term memory, and critical flicker fusion.² In one experiment, 15 male subjects were studied during 70-min exposures to approximately 100 or 300 ppm xylene vapor. In a second experiment, subjects were exposed for 70 min to 300 ppm xylene. This exposure period began with 30 min of work on a bicycle, during which muscular contraction was measured with an ergometer, and continued during the behavioral tests. In the first experiment, xylene did not cause any noticeable change in test performance when the subject's total uptake of xylene was estimated to average 540 mg for the 300 ppm exposures and 180 mg for the 100 ppm exposures. In the second experiment physical exercise resulted in an increase in the uptake of xylene to an average of 1,200 mg. In this experiment, significant performance decrements were observed in the tests of numerical ability, short-term memory, and choice reaction time.

Ogata et al. (1970) measured blood pressure, pulse rate, critical flicker fusion rate, and reaction time in 23 male subjects exposed for 3 or 7 hr to 100 ppm xylene or 100 and 200 ppm of xylene. They observed no significant changes in any of the tests.

Gusev (1968) studied the effects of xylene, benzene, and toluene on the electrical activity of the cerebral cortex. He exposed four subjects to xylene in concentrations of approximately 0.07 and 0.05 ppm. At the 0.07 ppm level, xylene reportedly produced a large change in brain electrical activity, whereas the 0.05 ppm exposures had no effect. As already remarked in the review of the literature on toluene, these values are far lower than those reported in other studies. In view of this inconsistency with the rest of the literature, these studies require replication.

Savolainen et al. (1979b) exposed six male subjects to m-xylene for 6 hr/day, 3 days/week for 2 weeks. In one part of the study constant levels of 100 or 200 ppm were used; in another part, the concentration was either 100 or 200 ppm as a time-weighted average, but the concentration was systematically varied so that peak concentrations of 400 ppm were obtained. Slight impairment of equilibrium and significant increases in reaction time were noted even at 100 ppm during the first week. These effects were not stable, suggesting the development of tolerance. However, effects were again apparent during the second week of exposure, particularly at the

²When the frequency of a flickering light is increased to the point that the light no longer appears to flicker, the term "flicker fusion" is applied.

higher concentrations. There were no significant changes in measurements of manual dexterity, flicker fusion, or extraocular muscle balance.

In a subsequent study, using essentially the same exposure schedules and concentrations of xylene, Savolainen *et al.* (1980) tested subjects and recorded electroencephalograms following 10-minute periods of exercise on a bicycle monitored by an ergometer. As in the previous study, acute changes in reaction time and equilibrium were observed early in the study, even at a 90 ppm concentration of xylene. Although the changes did not persist until the end of the first week of exposure, they were again observed during the second week. Light exercise appeared to counteract the effects of xylene. Changes in electroencephalograms at the higher levels of exposure (200 to 400 ppm, peak) consisted mainly of increased numbers of transient occipital slow waves, which the authors interpreted as an indication of decreased vigilance. Savolainen *et al.* (1980) reported that disturbances in equilibrium occurred in human subjects with blood xylene values of 30 μM /liter, a level that is found in subjects exposed to xylene vapor of 200 ppm or less.

Occupational Exposure. Reports on occupational exposures of humans contribute little information that is useful to assessments of the neurotoxic effects of xylene, not only because of their scarcity but also because of the unavoidable lack of quantification of the relationship between exposure and effect and the impurity of materials to which workers are usually exposed.

Glass (1961) described one worker who suffered an acute episode of dizziness, incoordination, nausea, and loss of appetite as a result of inhaling solvent fumes from paint mixing pots intermittently for 2 months. The solvent was composed of 75% xylene and 25% ethyl-, methyl-, and trimethylbenzenes. The concentration of solvent vapor at the top of the paint-mixing pots was estimated to have reached 350 ppm, although it is possible that this worker could have been exposed briefly to much higher concentrations.

Goldie (1960) described eight men who complained of headache, vertigo, gastric discomfort, dryness of throat, and a feeling of slight drunkenness while painting in an enclosed space. The paint they had been using was said to contain 80% xylene and 20% methylglycol acetate. One painter had an epileptiform seizure preceded by a prodrome beginning approximately 1 hr after leaving the workplace. He had been working with paints for 2 months and had a history suggesting an epileptic focus. The author suggested the possibility that exposure to xylene potentiates latent epilepsy. This

had also been suggested by Stocké (1929), who noted an increased frequency of seizures when a patient was exposed to xylene.

Morley et al. (1970) reported an accident involving three painters who had inhaled paint fumes in an enclosed space. They reported that the paint fumes were composed predominantly of xylene and that the estimated exposure to xylene was 10,000 ppm. One man died, and the other two remained unconscious for 15 and 18 hr. After recovering consciousness, these men were mentally confused and amnesic concerning events preceding the period of unconsciousness, but recovery was apparently rapid.

Forty-five men who had been involved for 0.5 to 6 years in the manufacture of xylene from gasoline were studied by Sukhanova et al. (1969). Exposure levels in this study were no greater than approximately 45 ppm (U.S. National Institute for Occupational Safety and Health, 1975). The investigators presented no quantitative data on these workers or control subjects, but reported that approximately one-third of the 45 workers complained of headache, insomnia, irritability, tachycardia, and dyspepsia. They reported other "alterations" in the nervous system, but did not describe or quantify them.

Clinical Toxicology

Occupational exposures to xylene usually occur through inhalation, although some cases of percutaneous absorption have also been reported. The intake and metabolism are discussed in Chapter 5, and toxic effects of xylene are discussed earlier in this chapter. The toxicity of xylene in humans has been thoroughly reviewed by the U.S. National Institute for Occupational Safety and Health (1975).

Xylene has a relatively distinct odor and an odor threshold ranging from 0.14 to 1.4 ppm. Continuous inhalation of xylene has resulted in olfactory fatigue, but recovery occurs shortly after cessation of exposure (Carpenter et al., 1975). Irritation of the eyes and mucous membranes has been observed during acute exposure to 100 ppm or greater. Some investigators have suggested that there are reversible corneal effects in workers exposed to xylene (Schmid, 1956).

The major toxic effects of xylene in humans occur in the central nervous system. They begin with weakness and unsteadiness, and then progress to paralysis and, eventually, death. Early reports suggesting that xylene produced hematopoietic toxicity undoubtedly reflect exposure to benzene. Recent evidence clearly indicates that xylene alone does not cause hematological toxicity. However, the extent to which inhalation of xylene might alter the metabolism or toxicity of benzene in humans is unclear.

Direct contact with xylene produces irritation of the skin and mucous membranes. Inhalation leads to various nonspecific symptoms, including malaise, headache, weakness, lassitude, nausea, irritability, and loss of appetite, which clear rapidly following cessation of exposure. Significant neurologic, hematologic, cardiac, gastrointestinal, hepatic, and renal toxicities have also been reported to result from exposure to xylene, although in many cases these effects may have been caused by a compound in the solvent mixture other than xylene.

Although the effects of xylenes on the central nervous system are somewhat similar to those produced by other alkyl benzenes, death due to narcosis has rarely been reported. Morley et al. (1970) described three workmen who had been exposed to an estimated 10,000 ppm xylene and much lower concentrations of toluene and other unidentified substances while painting an enclosed space. When found, approximately 18 hr after beginning the painting, one individual was dead. Necropsy revealed pulmonary edema, focal intraalveolar hemorrhage, microscopic brain hemorrhages, and anoxic neuronal damage. The liver was congested with swelling and vacuolation of cells primarily in the centrilobular area. The other two workmen were unconscious, and one was hypothermic (body temperature 32.2°C). Slight elevation of serum glutamic oxaloacetic transaminase, which was observed in both patients, suggested mild impairment of the liver. Enzyme activity returned to normal within a few days. Renal damage, which was observed only in the hypothermic patient, may have been a result of his clinical condition rather than a direct effect of xylene. Both had mild persistent amnesia and were confused or ataxic during recovery.

Summary

The acute toxicity of the xylenes predominantly reflects effects on the central nervous system similar to those produced by other alkyl benzenes and related compounds. Irritant effects on mucous membranes have been reported, particularly upon direct contact. There is negligible evidence of acute or chronic effects in organ systems other than the central nervous system.

ETHYLBENZENE

As indicated by the following discussion, studies to examine the toxicity of ethylbenzene have been limited.

Acute Exposure to Ethylbenzene

Wolf et al. (1956) determined that the oral LD₅₀ for ethyl

body weight. The animals were observed for 2 weeks after a single administration of the compound. In another study, Smyth et al. (1962) found that the acute oral LD₅₀ in rats was 5.46 ml/kg (5.09-5.86 ml/kg). The single skin penetration LD₅₀ for rabbits was reported to be 17.8 ml/kg in one study (Smyth et al., 1962) and greater than 5 g/kg in another (Moreno, 1974).

Ethylbenzene produced irritation when applied to the uncovered rabbit belly (Smyth et al., 1962). When applied in full strength to intact or abraded skin for 24 hr under occlusion, it was moderately irritating (Moreno, 1974). Ethylbenzene does not appear to be a sensitizing chemical. A maximization test (Kligman, 1966; Kligman and Epstein, 1975) conducted on 25 volunteers at a concentration of 10% in petrolatum produced no sensitization reactions (Kligman and Epstein, 1975).

Subchronic Exposure to Ethylbenzene

Wolf et al. (1956) also performed subchronic studies on rats, rabbits, guinea pigs, and monkeys exposed to ethylbenzene by various routes. Female rats exhibited histopathological changes in the liver and kidneys when a total dose of 408 mg/kg body weight ethylbenzene was administered via stomach tube over 6 months. In rabbits, dermal application of pure ethylbenzene caused a slight irritation, whereas the intraocular application of two drops of ethylbenzene caused transient corneal damage. Inhalation of 600 ppm (2.6 g/m³) ethylbenzene adversely affected the livers, kidneys, and testes of all animals treated. No adverse effects in the hematopoietic system were observed in any of the animals.

Chronic Exposure to Ethylbenzene

The committee found no data on chronic exposure to this compound.

Summary

Only a few studies have been conducted to test the toxicity of ethylbenzene. Because of the limited information on acute and subchronic exposure to ethylbenzene and the lack of data pertaining to chronic exposure, it is difficult to make a definitive statement regarding the toxicity of this compound.

CUMENE

There is relatively little information concerning the toxicology of cumene. Much of it comes from a series of studies by Gerarde (1959).

and other studies, which compare the toxicity of various alkyl compounds. A major aim of these studies was to develop an understanding of the relationship between specific alkyl groups and the properties of the compounds.

Acute Exposure to Cumene. Among the earlier studies of cumene toxicity are those of Lazere (1929) who reported that mice became prostrate after inhaling 4,080 ppm and lost reflexes after inhaling 5,700 ppm. Werner et al. (1944) reported an LC_{50} of 10.0 mg/liter in mice exposed for 7 hr to a "relatively pure" cumene. In a repeated study in somewhat older mice (27 g vs 21 g), the LC_{50} was 11.5 mg/liter, suggesting possible resistance with age. A technical grade cumene (>95%) produced similar effects. The mice were described as manifesting a slight lack of coordination followed by narcosis, complete relaxation, loss of reflexes, decreased respiration, and death. Narcosis lasted up to 36 hr in surviving animals. Pathological findings were noted for slight fatty infiltration of the liver, particularly in centrilobular areas, and some fatty droplets in renal cells. There was no evidence of pulmonary irritation.

Wolf et al. (1956) compared the toxicity of various alkyl benzenes and benzene. Studies of acute effects following the administration of a single oral dose of cumene to rats revealed an LD_{50} of 1.4 g/kg body weight. The range for the other eight compounds studied was 1.2 g/kg (diethylbenzene) to 7.0 g/kg (toluene). Pathological examination revealed slight changes in the liver. Cumene was shown to act as having produced some irritation to the stomach and intestines. Female rats were given 139 oral doses of cumene over 194 days at 462, or 769 mg/kg body weight per dose. No effects on weight or hematological or histopathological indices were noted at 154 mg/kg. At the two higher concentrations, only a dose-related increase in kidney weight was observed.

Wolf et al. (1956) also studied the effects of repeated applications of cumene to rabbit skin. They observed erythema and slight necrosis but no evidence of acute toxicity resulting from the applications. Instillation of cumene into the rabbit eye produced conjunctival irritation but no corneal damage.

After administering a single oral dose of cumene to rats, Smith and Smyth (1928) reported an LD_{50} of 2.91 g/kg body weight, approximately twice that observed by Wolf et al. (1956). The 95% confidence limits of their data are given as 2.55-3.32 g/kg. They also reported an LD_{50} for penetration of rabbit skin of 12.3 ml/kg and the 95% confidence limits as 7.69 - 19.7 ml/kg. Inhalation of 8,000 ppm cumene for 4 hr led to the death of four of six rats. The same investigators observed mild skin irritation but no eye irritation in direct contact studies with rabbits.

In the Soviet Union, Gorban et al. (1978) described studies of mice, rats, and rabbits that were exposed to cumene by various routes. They reported that cumene concentrated in fatty tissues and that it produced a local irritative effect when applied to the conjunctiva or skin. Inhalation of $1,000 \text{ mg/m}^3$, apparently for 4 hr, led to effects on the central nervous system, pathological changes, leukocytosis, reticulocytosis, and an increase in blood coagulability. Only the hematological effects were said to be present at 360 mg/m^3 . The authors concluded that this concentration is close to the threshold level.

Summary

The literature provides little information on the toxicity of cumene. Of importance to the effects of cumene is that it has a larger alkyl constituent than xylene, toluene, or ethylbenzene, and its side chain is branched. The studies of Valette and Carvier (1954) suggest that branching of the side chain tends to increase skin absorption (Gerarde, 1959). Cumene penetrated percutaneously more readily than did p-cumene, toluene, p-xylene, and ethylbenzene, in that order. It is said to produce a painful sensation if placed on the tongue, and it is generally a mucous membrane irritant.

Its low vapor pressure has both positive and negative toxicological implications. In contrast to benzene and toluene, its vapor concentrations will be lower near an open vat or spill of cumene. However, once intoxication occurs, the cumene will be less rapidly lost by exhalation.

EPIDEMIOLOGICAL STUDIES

Epidemiological studies attempt to show statistical association between common experience of groups of persons and their subsequent biological responses. The major problems encountered in such studies of exposures to alkyl benzenes are related to quantification and specificity of the exposures, which often involve more than one compound, and, in most instances, can be estimated only by ordinal scaling; i.e., by rank order of exposure.

Sterner (1941) studied the hazards encountered indoors during spray painting when gasoline was used as the diluent. The concentrations of toluene and xylene in this gasoline were usually between 5% and 10%, but ranged as much as 1% to 30%. Concentrations of aromatic hydrocarbons between 300 and 800 ppm were measured in the area of the spray-painting activity. Although protected with a cartridge-type respirator, workmen exposed to these concentrations showed evidence of toxic effects. Their symptoms were headache,

nausea, weakness, mental depression, anorexia, and inability to sustain attention and activity. The accompanying laboratory findings indicated that there were also decreases in hemoglobin erythrocyte, and cell volumes and increases in mean corpuscular hemoglobin, mean corpuscular volume, and reticulocyte count. There was no long-term followup of these workers to determine specific causes of death and to learn if they developed unusual frequency of chronic illness or neoplasms at similar sites.

In 1970, the rubber workers' union stimulated the commissioning of studies at the University of North Carolina and the Harvard University School of Public Health. At North Carolina, McMichael et al. (1975) demonstrated an association of lymphatic leukemia in rubber workers with a history of exposure to organic solvents. The organic solvents most commonly used in the rubber industry include benzene, xylene, toluene, trichloroethylene, and various aliphatic hydrocarbons (McMichael et al., 1976). The investigators found the association by examining causes of death within occupational groups since actual exposure data were not available. Thus, the exposures are not specific but are implied by the job title.

For some years, rotogravure printers have been concerned about their exposure to solvents. Bänfer (1961) examined the peripheral blood cellular effects of exposure to toluene containing 0.3% benzene in 889 rotogravure printers and helpers compared to 478 unexposed subjects in the same industry. The highest concentration of toluene to which the workers were exposed was 400 ppm. This occurred infrequently and in just a few of the areas within the plant. No estimate of long-term average exposures was provided. Effects on the formed elements of blood in the exposed group were no different from those in the controls. No pathologic changes in the bone marrow were found in six sternal biopsies.

In 1972, the West German Association of Gravure Printers concluded that there were few facts on which to base any judgment regarding the effects on humans resulting from exposure to toluene (Suhr, 1975). Since toluene containing 0.3% benzene had been available and in use since 1955, there were gravure printers with years of exposure who could be studied to ascertain if there were identifiable manifestations from that exposure. A study population of 100 persons was identified with at least 10 years of exposure; a control group of a similar size. Suhr (1975) stated explicitly that the controls had been with the company for 10 years; however, the figure in his report indicated that eight persons in the study had been employed by the company less than 10 years. This implies there was no strict adherence to admission criteria. Analysis of samples collected from the work area indicated that potential exposure to toluene ranged from 200 to 400 ppm. The neurologic tests, the laboratory diagnostic tests, and blood analyses demon-

strated no unusual frequency of abnormalities in either the study or control groups, but approximately half of each group had abnormal liver enzyme tests. The symptoms involving the central nervous system did not correlate with exposure. The author concluded, "The state of health of the toluene exposed test persons was in no way different from that of the control group. Neither clinical nor laboratory diagnosed grounds for liver damage in long term exposed persons, nor signs of toxic effects on the central nervous system could be found."

Stern and Oser (1979) reviewed the criteria document Occupational Exposure to Xylene (U.S. National Institute for Occupational Safety and Health, 1975). They reported that epidemiological studies of exposure to xylene do not exist. Lob (1952) studied 19 photogravure workers who had been exposed to ink-diluent vapors. These vapors certainly contained hydrocarbons such as toluene and benzene in addition to xylene. Therefore, it is difficult to conclude much from this study.

Sukhanova et al. (1969) studied 45 young to middle-aged men who manufactured xylene from gasoline. Exposures in this study also contained hydrocarbons in addition to xylene. However, 35% to 40% of the samples contained approximately 10 ppm xylene, and the concentrations in some samples reached levels as high as approximately 45 ppm. "On being questioned, approximately one-third of the workers complained of occasional headaches, insomnia, irritability, tachycardia and dyspepsia." In nine workers (20%), nervous system alterations of the type of "neurasthenic or asthenoaautonomic syndromes" were diagnosed, and "autonomic-vascular dysfunction" was observed in six (13%). There were no other significant symptoms. These potentially psychosomatic clinical findings were not compared with the incidence in a control population to ascertain if they were peculiar to the exposure. "The amount of phenols excreted in the urine was higher than normal in all cases. There were no changes in the erythrocyte, reticulocyte or thrombocyte counts or in hemoglobin." Both the glycogen and peroxidase contents of neutrophils were found to be decreased in comparison with controls, and the decrease became more pronounced with increased duration of exposure.

Summary

The epidemiological studies are few in number, small in terms of exposed population size, nonspecific with regard to alkyl benzene exposure, and mostly negative in terms of significant findings. Where there were suggested effects, there were other exposures that complicated the interpretation of the role of the alkyl benzenes present. Although these studies provide some assurance that alkyl

benzenes do not have deleterious effects in concentrations to which populations might be exposed, they are far from reassuring that effects will result from long-term, low-level exposure.

GENETIC EFFECTS

Short-term bioassays are assuming greater importance in the evaluation of genetic properties of a test chemical. The recent suggestion that benzene produces leukemia has stimulated extensive investigations of the clastogenic properties of the aromatic hydrocarbon solvents and limited studies of their ability to induce gross or point mutations.

This section attempts to assess the mutagenic potential of some alkyl derivatives of benzene.

Toluene

Mutagenic Potential. The genetic properties of toluene have recently been evaluated in a battery of short-term mutagenicity assays consisting of a test for mitotic gene conversion in the yeast Saccharomyces cerevisiae D4, gene mutation tests in several bacterial strains (Salmonella typhimurium TA98, TA100, TA1535, TA1537, and TA1538) with and without activation, and specific locus forward mutation induction in the L5178Y thymidine kinase Fischer mouse lymphoma cell assay (Litton Bionetics, Inc., 1978a). The results of all microbial tests (with bacteria and yeast) and the mouse lymphoma assay were negative. However, the results of bacterial tests were somewhat varied because of the extreme toxicity of toluene to these organisms.

Toluene, a strongly lipophilic solvent, has also been used to reduce the permeability of bacterial cell walls (Miller *et al.* 1973; Moses and Richardson, 1970; Sullivan and Volcani, 1976). Toluene-treated strains of Escherichia coli are more permeable to low molecular weight compounds such as deoxynucleoside triphosphates than are untreated bacteria (Moses and Richardson, 1970). This suggests that highly lipophilic solvents such as toluene might influence the penetration of test compounds into bacteria if it is used as a solvent in microbial mutation tests (Dean, 1977).

Clastogenic Potential. A daily subcutaneous injection of 8 to 11.0 mmol (0.8-1.0 g) of toluene per kilogram body weight for 12 days caused an increased frequency (13.7%) of chromosome damage in the bone marrow cells of rats, compared to a frequency of 4.2% in a control group. The chromatid gaps were the most common change detected in bone marrow cells from toluene-treated rats (Lyapkalo, 1973).

The persistence of chromosome aberrations in rats after an inhalation exposure to toluene was described by Dobrokhotov and Enikeev (1977). The animals were exposed 4 hr daily for 4 months to 610 mg of toluene per cubic meter of air or to 610 mg of toluene plus 300 mg benzene per cubic meter of air. During this exposure, the percentage of metaphases with damaged chromosomes in the bone marrow of the rats increased gradually to 21.56% (toluene) and 41.21% (toluene plus benzene) compared to 4.02% in controls. In addition, both toluene and the mixture of toluene and benzene caused leukosis. One month after the termination of the inhalation, chromosome damage was still frequent, whereas the morphological composition of blood had almost returned to normal. In another 12-day study, Dobrokhotov (1972) estimated that toluene administered subcutaneously to rats in doses of 0.8 g/kg/day induced the same frequency of chromosome damage as benzene in doses of 0.2 g/kg/day.

Cytogenetic examination of lymphocytes in printers exposed to toluene from 1953 to 1968 (Forni et al., 1971) and a recent study of 32 male rotogravure workers (Mäki-Paakkanen et al., 1980) revealed no significant increase in the number of chromosome aberrations when the groups were compared with controls. Atmospheric concentrations of toluene from 1953 to 1968 were generally close to 200 ppm, although workers were occasionally exposed to much higher concentrations. In light of the apparent absence of chromosome damage in humans and the exceedingly high concentrations of toluene required to induce chromosome aberrations in animals, Dean (1977) concluded that the current threshold limit value of 100 ppm (American Conference of Governmental Industrial Hygienists, 1978) was most likely to afford protection against chromosome damage from occupational exposure.

Xylenes

Xylene (nature of the isomer not mentioned) was not mutagenic in a battery of short-term tests: a test for mitotic gene conversion in yeast Saccharomyces cerevisiae D4, gene mutation tests in bacteria (using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538) with and without activation, and specific locus forward mutation induction in the L5178Y thymidine kinase Fischer mouse lymphoma cell assay. Also, xylene did not produce significant increases in chromosome aberrations in rat bone marrow cells at levels of 0.044, 0.147, and 0.441 ml/kg body weight (Litton Bionetics Inc., 1978b).

Ethylbenzene

There is no report on the mutagenicity of ethylbenzene. However, Salmona et al. (1976) have shown that the four common metabolites

of ethylbenzene (D and L mandelic, phenylglyoxylic, and hippuric acids) give negative results in the Ames test using five Salmonella typhimurium strains: TA1535, TA1537, TA1538, TA100, and TA98.

Cumene (Isopropylbenzene)

In a report prepared for the U.S. Environmental Protection Agency, Simmon and Kauhanen (1978) reported that Stanford Research Institute International examined cumene for mutagenic activity with tester strains TA1535, TA1538, TA100, and TA98 of Salmonella typhimurium in the Ames Salmonella microsome assay (using both the standard desiccator techniques) and with the yeast Saccharomyces cerevisiae. Each assay was performed both in the presence and in the absence of a metabolic activation system (Aroclor-1254-induced rat liver homogenate). Cumene showed no mutagenic activity when subjected to these procedures.

TERATOGENICITY

There have been very few studies on teratogenicity of benzene and its alkyl derivatives, even though these solvents have been included among chemicals suspected of having such an effect (Kunz 1976; Yager, 1973).

Toluene, Xylenes, and Ethylbenzene

A connection between the occurrence of sacral aplasia and occupational exposure to organic solvents has been demonstrated by Kučera (1968), who also observed a developmental malformation analogous to sacral aplasia in chick embryos treated with xylene. Krotov and Chebotar (1972) did not find any developmental defect in fetuses of rats that had inhaled xylene. In a study of inhalation exposures by Hudák and Ungváry (1978), the embryotoxic effects of benzene and its derivatives, such as toluene and xylene (a mixture of 10% o-xylene, 50% m-xylene, 20% p-xylene, and 20% ethylbenzene), were evaluated. CFY outbred rats were exposed to 1,000 mg/m³ benzene, 1,500 mg/m³ toluene, or 1,000 mg/m³ xylene for 24 hr/day from day 1 to day 21 of pregnancy. CFLP outbred mice were exposed to 500 mg/m³ toluene for 24 hr/day from day 6 to day 13 of pregnancy. Untreated groups of animals inhaling pure air served as controls. None of the solvents were proven to be teratogenic. However, an increase in skeletal anomalies (extra ribs, fused sternbrae) was observed after exposures to all three solvents. Benzene and toluene also caused retardation of fetal development.

In a recent report by Litton Bionetics, Inc. (1978c), pregnant female rats were exposed to graded airborne concentrations (100 and 400 ppm) of toluene on days 6 through 15 of gestation. In the dams there were no changes to indicate an adverse, compound-related effect, nor was there evidence of variation in fetal sex ratio, embryo toxicity, inhibition of fetal growth and development, or teratogenicity induced by toluene at these airborne concentrations.

Elovaara et al. (1979) injected toluene into the air space in fertilized chicken eggs in the second, third, and sixth days of incubation. Embryotoxicity was evaluated as incidence of survival and death after 14 days of incubation. The lengths of the embryos were also recorded. The "approximate LD₅₀" for toluene was more than 100 $\mu\text{mol/egg}$. Although the authors noted macroscopic malformations of various kinds at dose levels of 5 to 100 $\mu\text{mol/egg}$, the data demonstrate that only 1 of 46 displayed profound edema and 3 of 46 had skeletal abnormalities.

Euler (1967) reported that women working with a solvent containing toluene and trichloroethylene (mean daily dose, 372 mg/kg and 405 mg/kg, respectively) gave birth to multiply deformed children. Exposure of mice to the same solvent (mean daily dose, 157 mg/kg of toluene and 406 mg/kg of trichloroethylene) during gestation caused no malformations, but a weight reduction of the fetus at delivery, a decrease in rate and length of gestation, and unspecified damage to the ova were observed.

A recent study by Hunter et al. (1979) raised the possibility that inhalation of gasoline during pregnancy may be teratogenic in humans. They studied two infants from Shamattawa, a small community of American Indians in Manitoba, Canada, in which gasoline sniffing and alcohol abuse were known to be widespread. These children exhibited profound retardation, initial hypotonia progressing to hypertonia, scaphocephaly, a prominent occiput, poor postnatal head growth, and additional minor anomalies. These authors concluded that there was an excess of children born with severe and profound retardation in Shamattawa from 1973 to 1977. This might have been due to the action of one or more recessive genes. But the two children described in this study were born of mothers who inhaled leaded gasoline during pregnancy. Based on these limited observations, the authors suggested that the gross anomalies in the offspring may either be due to the teratogenic effect of leaded gasoline, to the recessive genes, or to a combination of both.

Summary

Toluene, xylene, and cumene are not mutagenic in the Ames Salmonella/microsome assay using the five Salmonella typhimurium

strains TA98, TA100, TA1535, TA1537, and TA1538, with and without metabolic activation system (using Aroclor-1254-induced rat liver homogenate). Moreover, toluene and xylene do not show mutagenicity in a battery of other short-term bioassays such as a test for mitotic-gene conversion in the yeast Saccharomyces cerevisiae D4 and specific locus forward mutation induction in the L5178Y thymidine kinase mouse lymphoma cell assay. The only evidence for genetic effects of toluene was the observation of increased chromosome aberration in rats; however, this was not observed in study with humans.

With regard to teratogenicity, solvents such as toluene, xylene, and ethylbenzene are embryotoxic to chicks. An increase in skeletal anomalies such as extra ribs and fused sternbrae has also been observed in rats and mice. None of these solvents has been proved to be teratogenic.

GENERAL CONCLUSIONS

The naturally occurring alkyl benzenes covered in this report--toluene, ethylbenzene, cumene, and xylenes--all produce narcosis. The LD₅₀ values for these compounds are high, indicating that the toxicity of the alkyl benzenes is relatively low. Glue sniffing, often involving inhalation of toluene, has become a well-known problem. It has been associated with the "sudden sniffing death" syndrome and may be related to cardiac arrhythmias caused by toluene.

Studies of xylene and toluene indicate that the alkyl benzenes considered in this report have a low order of toxicity. Although people exposed occupationally may be at some risk, there appears to be little danger of adverse effects in the general population as a result of current or projected ambient levels of exposure. In the absence of quantitative toxicological data concerning the effects and mechanisms of action of individual alkyl benzenes and combinations thereof, it is safest to assume that the actions of combinations of two or more of these substances on the nervous system are at least additive.

Evaluations of the teratogenetic potential of the alkyl benzenes indicate that they may have mild embryotoxic effects. The naturally occurring alkyl benzenes are not mutagenic in the Ames test, but toluene increases chromosomal aberrations in rats. However, these aberrations were not observed in printers exposed for 15 years. The carcinogenic potential of toluene, the xylenes, ethylbenzene, and cumene has not been examined via long-term bioassays.

Nevertheless, our knowledge of the biochemical mechanisms of action is still quite fragmentary. Therefore, decisions concerning

safe levels of exposure must be recognized as "best judgments" that lack any great degree of precision.

Clinical exposure to alkyl benzenes occurs mainly among adolescents through deliberate inhalation of "glue" or solvents, which commonly contain toluene. Although sudden death due to solvent sniffing has been reported in a number of cases, and neurological, hematological, renal, and metabolic effects have been associated with glue sniffing, it appears that alkyl benzenes play a relatively minor role in nonfatal toxicity due to solvent sniffing. Furthermore, the variable composition of the glue and the presence of a number of other hydrocarbons besides alkyl benzenes cloud the interpretation of the data.

Epidemiological studies offer few data and are inconclusive.

REFERENCES

- Alha, A., T. Korte, and M. Teahu. 1973. Solvent sniffing death.
Z. Rechtsmed. 72:299-305.
- American Conference of Governmental Industrial Hygienists. 1978.
TLVs®: Threshold Limit Values for Chemical Substances and
Physical Agents in the Workroom Environment with Intended
Changes for 1978. American Conference of Governmental Indus-
trial Hygienists, Cincinnati, Ohio. 94 pp.
- Anderson, P., and B. R. Kaada. 1953. The electroencephalogram
in poisoning by lacquer thinner (butyl acetate and toluene).
Acta Pharmacol. Toxicol. 9:125-130.
- Andrews, L. S., E. W. Lee, C. M. Witmer, J. J. Kocsis, and R. Snyder.
1977. Effects of toluene on the metabolism, disposition and
hemopoietic toxicity of [³H]benzene. Biochem. Pharmacol. 26:
293-300.
- Astrand, I., H. Ehrner-Samuel, Å. Kilbom, and P. Övrum. 1972.
Toluene exposure. I. Concentration in alveolar air and
blood at rest and during exercise. Work Environ. Health 9:
119-130.
- Axelsson, O., M. Hane, and C. Hogstedt. 1976. A case-referent
study on neuropsychiatric disorders among workers exposed
to solvents. Scand. J. Work Environ. Health 2:14-20.
- Bänfer, W. 1961. Untersuchungen über Einwirkung von Reintoluol
das Blutbild von Druckern und Hilfsarbeitern im Tiefdruck.
(Investigation of the effect of pure toluene on the blood pi-
ture of rotogravure printers and auxiliary workers.) Zentra-
Arbeitsmed. Arbeitsschutz. 11:35-40. [Bulletin of Hygiene 3
640-641, 1961.]
- Barman, M. L., N. B. Siegel, D. B. Beedle, and R. K. Larson. 1968.
Acute and chronic effects of glue sniffing. Calif. Med. 100:
19-22.
- Barnes, G. E. 1979. Solvent abuse: A review. Int. J. Addict.
1-26.
- Bass, M. 1970. Sudden sniffing death. J. Am. Med. Assoc. 212:
2075-2079.

- Batchelor, J. J. 1927. The relative toxicity of benzol and its higher homologues. *Am. J. Hyg.* 7:276-298.
- Battig, K., and E. Grandjean. 1964. Industrial solvents and avoidance conditioning in rats. A comparison of the effects of acetone, ethyl alcohol, carbon disulfide, carbon tetrachloride, toluene, and xylene on acquisition and extinction. *Arch. Environ. Health* 9:745-749.
- Beirne, G. J., and J. T. Brennan. 1972. Glomerulonephritis associated with hydrocarbon solvents. *Arch. Environ. Health* 25: 365-369.
- Bereznyi, E. A., I. E. Shvartsman, N. S. Shlyakhetskii, I. Turay, and A. Sidorenko. 1975. Method for the evaluation of electrocardiograms in toxicological experiments using a heart rhythm histogram series. *Tr. Leningr. Sanit.-Gig. Med. Inst.* 111:73-79. [Chem. Abs. 89:101048q, 1978.]
- Bernshtein, L. M. 1972. Phagocytosis reaction in experimental animals on chronic poisoning by vapors of benzene and its methyl derivatives. Pp. 53-54 in *Vop. Gig. Tr. Profzabol., Mater. Nauch. Konf.* 1971. [Chem. Abs. 81:146520p, 1974.]
- Bloch, B., and G. Tadjer. 1975. [Fatal inhalation of fumes of contact glue.] *Harefuah* 89(2):74-75. [Cumulated Index Medicus 17: 1598, 1976.]
- Bonnet, P., G. Raoult, and D. Gradiski. 1979. (English summary) Concentrations léthals 50 des principaux hydrocarbures aromatiques. (Lethal concentration 50 of main aromatic hydrocarbons.) *Arch. Mal. Prof. Med. Trav. Secur. Soc.* 40:805-810.
- Boor, J. W., and H. I. Hurtig. 1977. Persistent cerebellar ataxia after exposure to toluene. *Ann. Neurol.* 2:440-442. [Cumulated Index Medicus 20:1553, 1979.]
- Bruckner, J. V., and R. G. Peterson. 1976. Evaluation of toluene toxicity, utilizing the mouse as an animal model of human solvent abuse. *Pharmacologist* 18:244 (Abstract 713).
- Cameron, G. R., J. L. H. Paterson, G. S. W. de Saram, and J. C. Thomas. 1938. The toxicity of some methyl derivatives of benzene with special reference to pseudocumene and heavy coal tar naphtha. *J. Pathol. Bacteriol.* 46:95-107.
- Capellini, A., and L. Alessio. 1971. L'eliminazione urinaria di acido ippurico in operai esposti a toluolo. (The urinary excretion of hippuric acid in workers exposed to toluene.) *Med. Lavoro* 62:196-201.

- Capurro, P. U. 1976. Hydrocarbon exposure and cancer. *Lancet* 253:254.
- Carpenter, C. P., C. B. Shaffer, C. S. Weil, and H. F. Smyth. 1944. Studies on the inhalation of 1:3-butadiene; with a comparison of its narcotic effect with benzol, toluol, and styrene, and a note on the elimination of styrene by the J. Ind. Hyg. Toxicol. 26(3):69-78.
- Carpenter, C. P., E. R. Kinkead, D. L. Geary, Jr., L. J. Sullivan, and J. M. King. 1975. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylenes. *Toxicol. Appl. Pharmacol.* 33:543-558.
- Carpenter, C. P., D. L. Geary, Jr., R. C. Myers, D. J. Nachreiner, L. J. Sullivan, and J. M. King. 1976. Petroleum hydrocarbon toxicity studies. XIII. Animal and human response to vapors of toluene concentrate. *Toxicol. Appl. Pharmacol.* 36:473-483.
- Chenoweth, M. B. 1946. Ventricular fibrillation induced by hydrocarbons and epinephrine. *J. Ind. Hyg. Toxicol.* 28:151-155.
- Dean, B. J. 1977. Genetic toxicology of benzene, toluene, xylene, and phenols. *Mutat. Res.* 47:75-97.
- Dési, I., F. Kovács, Z. Zahumenszky, and A. Balogh. 1967. Memory learning in rats exposed to xylene intoxication. *Psychopharmacologia* 11:224-230.
- Divincenzo, G. D., and W. J. Krasavage. 1974. Serum ornithine carbamyl transferase as a liver response test for exposure to organic solvents. *Am. Ind. Hyg. Assoc. J.* 35:21-29.
- Dobrokhoto, V. B. 1972. Mutagenic action of benzene and toluene under experimental conditions. *Gig. Sanit.* No. 10:36-39. [Chem. Abs. 78:80464c, 1973.]
- Dobrokhoto, V. B., and M. I. Enikeev. 1977. Mutagenic effects of benzene, toluene, and a mixture of these hydrocarbons in a chronic experiment. *Gig. Sanit.* 1:32-34 (CA:86:84355f, 1977).
- Elovaara, E., K. Hemminki, and H. Vainio. 1979. Effects of methylene chloride, trichloroethane, trichloroethylene, tetrachloroethylene and toluene on the development of chick embryos. *Toxicology* 12:111-119.
- Euler, H. H. 1967. Tierexperimentelle Untersuchung einer Industrie-Noxe. *Arch. Gynaekol.* 204:258-259.

- Fabacher, D. L., and E. Hodgson. 1977. Hepatic mixed-function oxidase activity in mice treated with methylated benzenes and methylated naphthalenes. *J. Toxicol. Environ. Health* 2: 1143-1146.
- Falck, B., and H. Möller. 1963. Catecholamines of skin treated with organic solvents and ultraviolet light. *Acta Derm. Venereol.* 43:480-484.
- Ferguson, J. 1939. The use of chemical potentials as indices of toxicity. *Proc. Roy. Soc. London Ser. B* 127:387-404.
- Fischman, C. M., and J. R. Oster. 1979. Toxic effects of toluene. A new cause of high anion gap metabolic acidosis. *J. Am. Med. Assoc.* 241:1713-1715.
- Forni, A., E. Pacifico, and A. Limonta. 1971. Chromosome studies in workers exposed to benzene or toluene or both. *Arch. Environ. Health* 22:373-378.
- Frentzel-Beyme, R., A. M. Thiess, and R. Wieland. 1978. Survey of mortality among employees engaged in manufacture of styrene and polystyrene at the BASF Ludwigshafen works. *Scand. J. Work Environ. Health* 4(Suppl. 2):231-239.
- Friborská, A. 1973. Some cytochemical findings in the peripheral white blood cells in workers exposed to toluene. *Folia Haematol. (Leipzig)* 99:233-237.
- Furnas, D. W., and C. H. Hine. 1958. Neurotoxicity of some selected hydrocarbons. *AMA Arch. Ind. Health* 18:9-15.
- Gamberale, F., and M. Hultengren. 1972. Toluene exposure II. Psychophysiological functions. *Work Environ. Health* 9:131-139.
- Gamberale, F., G. Annwall, and M. Hultengren. 1978. Exposure to xylene and ethylbenzene. III. Effects on central nervous functions. *Scand. J. Work Environ. Health* 4:204-211.
- Geller, I., S. Randle, and R. Hartmann. 1978. Effects of acetone and toluene on fixed-ratio, fixed-interval responding in the rat. *Pharmacologist* 20:224 (Abstract 404).
- Gerard, H. W. 1959. Toxicological studies on hydrocarbons. III. The biochemorphology of the phenylalkanes and phenylalkenes. *AMA Arch. Ind. Health* 19:403-418.
- Glass, W. I. 1961. Annotation: A case of suspected xylol poisoning. *N. Z. Med. J.* 60:113.

- Goldie, I. 1960. Can xylene (xylol) provide convulsive se
Ind. Med. Surg. 29:33-35.
- Gorban, G. M., G. I. Solomin, Yu. P. Bizin, N. F. Sopikov,
Tikhonova, V. M. Zinov'ev, Z. I. Pilipyuk, A. I. Gorsh
and E. I. Chukhno. 1978. Study of the toxicity and o
of the threshold of the acute inhalation effect of iso
Gig. Sanit. No. 10:113. [Chem. Abs. 90:17136e, 1979.]
- Goto, I., M. Matsumura, N. Inoue, V. Murai, K. Shida, T. Sa
Y. Kuroiwa. 1974. Toxic polyneuropathy due to glue s
J. Neurol. Neurosurg. Psychiatry 37:848-853.
- Grabski, D. A. 1961. Toluene sniffing producing cerebella
generation. Am. J. Psychiatry 118:461-462.
- Greenburg, L. M. R. Mayers, H. Heimann, and S. Moskowitz.
The effects of exposure to toluene in industry. J. Am
Assoc. 118:573-578.
- Gusev, I. S. 1968. Comparative toxicity studies of benzer
toluol, and xylol by the reflex activity method. Pp.
in B. S. Levine, ed. U.S.S.R. Literature on Air Pollut
and Related Occupational Diseases, Volume 17. (Availa
the National Technical Information Service, Springfiel
Va., as PB-180522.)
- Gusev, I. S. 1972. The toxicology of low concentrations o
hydrocarbons. Pp. 19-34 and 124-128 (bibliography) in
Nuttonson, ed. AICE Survey of USSR Air Pollution Liter
Volume 15. American Institute of Crop Ecology, Silver
Md.
- Hänninen, H., L. Eskelinen, K. Husman, and M. Nurminen. 19
Behavioral effects of long-term exposure to a mixture
organic solvents. Scand. J. Work Environ. Health 2:24
- Harkonen, H. 1978. Styrene, its experimental and clinical
toxicology. Scand. J. Work Environ. Health 4(Suppl. 2
113.
- Hayden, J. W., R. G. Peterson, and J. V. Bruckner. 1977.
of toluene (methylbenzene): Review of current literat
Toxicol. 11:549-559.
- Holmberg, B., and T. Malmfors. 1974. The cytotoxicity of
organic solvents. Environ. Res. 7:183-192.

- Horiguchi, S., and K. Inoue. 1977. Effects of toluene on the wheel-turning activity and peripheral blood findings in mice. An approach to the maximum allowable concentration of toluene. J. Toxicol. Sci. 2:363-372.
- Horiguchi, S., K. Inoue, and M. Arisue. 1976. Studies on industrial toluene poisoning, part IV. Effects of toluene inhalation on wheel-turning activity and peripheral blood findings in mice. Sumitomo Sangyo Eisei 12:81-90. [Chem. Abs. 88:70139t, 1978.]
- Hudák, A., Z. Bors, and Gy. Ungvary. 1975. Experimental investigation of the histochemical study. Morphol. Igazságügyi Orv. Sz. 15:209-217.
- Hudák, A., and G. Ungváry. 1978. Embryotoxic effects of benzene and its methyl derivatives: toluene, xylene. Toxicology 11:55-63.
- Hunter, A. G. W., D. Thompson, and J. A. Evans. 1979. Is there a fetal gasoline syndrome? Teratology 20:75-80.
- Ikeda, M. 1974. Reciprocal metabolic inhibition of toluene and trichloroethylene in vivo and in vitro. Int. Arch. Arbeitsmed. 33:125-130.
- Ikeda, M., H. Ohtsuji, and T. Imamura. 1972. in vivo suppression of benzene and styrene oxidation by co-administered toluene in rats and effects of phenobarbital. Xenobiotica 2:101-106.
- Ikeda, T., and H. Miyake. 1978. Decreased learning in rats following repeated exposure to toluene: Preliminary report. Toxicol. Lett 1:235-239.
- Jenkins, L. J., R. A. Jones, and S. Siegel. 1970. Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol. Appl. Pharmacol. 16:818-823.
- Keane, J. R. 1978. Toluene optic neuropathy. Ann. Neurol. 4(4):390.
- Kelly, T. W. 1975. Prolonged cerebellar dysfunction associated with paint-sniffing. Pediatrics 56:605-606.
- Kimura, E. T., D. M. Ebert, and P. W. Dodge. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19:699-704.
- Kligman, A. M. 1966. The identification of contact allergens by human assay. III. The maximization test: A procedure for screening and rating contact sensitizers. J. Invest. Derm. 47:393-409.

- Kligman, A. M., and W. Epstein. 1975. Updating the maximization for identifying contact allergens. *Contact Dermatitis* 1:231-
- Knox, J. W., and J. R. Nelson. 1966. Permanent encephalopathy from toluene inhalation. *N. Engl. J. Med.* 275:1494-1496.
- Kojima, T., and H. Kobayashi. 1973. Toxicological study on toluene poisoning by inhalation. Correlation of toluene concentration for exposure with mortality and toluene tissue level. *Nippon Hoigaku Zasshi* 27:282-286.
- Korobkin, R., A. K. Asbury, A. J. Sumner, and S. L. Nielsen. 1975. Glue-sniffing neuropathy. *Arch. Neurol.* 32:158-162.
- Krivanek, N., and L. S. Mullin. 1978. Comparison of conditioned avoidance and unconditioned reflex tests in rats exposed by inhalation to carbon monoxide. *Toxicol. Appl. Pharmacol.* 45:357 (Abstract).
- Krotov, Y. A., and N. A. Chebotar. 1972. Embryotoxic and teratogenic action of some industrial substances formed during production of dimethylterephthalate. *Gig. Tr. Prof. Zabol* 16(6):40-43.
- Kučera, J. 1968. Exposure to fat solvents: A possible cause of sacral agenesis in man. *J. Pediatr.* 72:857-859.
- Kuntz, W. D. 1976. The pregnant women in industry. *Am. Ind. Hyg Assoc. J.* 37:423-426.
- Lange, A., R. Smolik, W. Zatonski, and J. Szymanska. 1973a. Serum immunoglobulin levels in workers exposed to benzene, toluene and xylene. *Int. Arch. Arbeitsmed.* 31:37-44.
- Lange, A., R. Smolik, W. Zatonski, and H. Glazman. 1973b. Leukocyte agglutinins in workers exposed to benzene, toluene and xylene. *Int. Arch. Arbeitsmed.* 31:45-50.
- Lazarew, N. W. 1929. Naunyn-Schmiedebergs (On the toxicity of various hydrocarbon vapors). *Arch. Exp. Pathol. Pharmacol.* 143:223-233.
- Lewis, P. W., and D. W. Patterson. 1974. Acute and chronic effects of the voluntary inhalation of certain commercial volatile solvents by juveniles. *J. Drug Issues* 4(2):162-175.
- Lindstrom, K. 1973. Psychological performances of workers exposed to various solvents. *Work Environ. Health* 10:151-155.

- Litt, I. F., M. I. Cohen, S. K. Schonberg, and I. Spigland. 1972. Liver disease in the drug-using adolescent. *J. Pediatr.* 81: 238-242.
- Litton Bionetics, Inc. 1978a. Mutagenicity Evaluation of Toluene. Final Report. Submitted to the American Petroleum Institute, Washington, D.C. in May 1978. LBI Project No. 20847. Litton Bionetics, Inc., Kensington, Md. 150 pp.
- Litton Bionetics, Inc. 1978b. Mutagenicity Evaluation of Xylene. Final Report. Submitted to the American Petroleum Institute, Washington, D.C. in May 1978. LBI Project No. 20847. Litton Bionetics, Inc., Kensington, Md. 150 pp.
- Litton Bionetics, Inc. 1978c. Teratology Study in Rats. Toluene. Final Report. Submitted to the American Petroleum Institute, Washington, D.C. in January 1978. LBI Project No. 20698-4. Litton Bionetics, Inc., Kensington, Md. 17 pp.
- Lob, M. 1952. L'intoxication chronique au toluol et au xylol et ses répercussions sur les organes hématopoiétiques. (Chronic intoxication with toluol and xylol; repercussions on hematopoietic organs.) *Schwiz. Med. Wochenschr.* 82:1125-1126. [Current List of Medical Literature 23:639, entry 39813, 1953.]
- Longley, E. O., A. T. Jones, R. Welch, and O. L. Sydney. 1967. Two acute toluene episodes in merchant ships. *Arch. Environ. Health* 14:481-487.
- Lorimer, W. V., R. Lilis, A. Fischbein, S. Daum, H. Anderson, M. S. Wolff, and I. J. Selikoff. 1978. Health status of styrene-polystyrene polymerization workers. *Scand. J. Work Environ. Health* 4(Suppl. 2):220-226.
- Lurie, J. B. 1949. Acute toluene poisoning. *S. Afr. Med. J.* 23:233-236.
- Lyapkalo, A. A. 1973. Genetic activity of benzene and toluene. *Gig. Tr. Prof. Zabol. No. 3*:24-28. [Chem. Abs. 79:1011x, 1973.]
- Mäki-Paakkanen, J., K. Husgafvel-Pursiainen, P.-L. Kalliomäki, J. Tuominen, and M. Sorsa. 1980. Toluene-exposed workers and chromosome aberrations. *J. Toxicol. Environ. Health* 6:775-781.
- Massengale, O. N., H. H. Glaser, R. E. LeLievre, J. B. Dodds, and M. E. Klock. 1963. Physical and psychologic factors in glue sniffing. *N. Engl. J. Med.* 269:1340-1344.

- Matsushita, T., Y. Arimatsu, A. Ueda, K. Satoh, and S. Nomura. 1975. Hematological and neuro-muscular response of work exposed to low concentration of toluene vapor. *Ind. Health* 13:115-121.
- McMichael, A. J., R. Spirtas, L. L. Kupper, and J. F. Gamble. Solvent exposure and leukemia among rubber workers: An epidemiologic study. *J. Occup. Med.* 17(4):234-239.
- McMichael, A. J., R. Spirtas, J. F. Gamble, and P. M. Tousey. Mortality among rubber workers: Relationship to specific agents. *J. Occup. Med.* 18:178-185.
- Meyer, H. 1899. Zur Theorie der Alkoholnarkose. Erste Mitteilung. Welche Eigenschaft der Anästhetica bedingt ihre narkotische Wirkung? *Arch. Exp. Pathol. Pharmacol.* 42:109-118.
- Meyer, K. H., and H. Hemmi. 1935. Beiträge zur Theorie der Narkose. *Biochem. Z.* 277:39-71.
- Miller, R. C., Jr., D. M. Taylor, K. MacKay, and H. W. Smith. Replication of T4 DNA in Escherichia coli treated with toluene. *J. Virol.* 12:1195-1203.
- Moreno, O. M. 1975. Report to RIFM, 1974. Food Cosmet. Toxicol. 13:803-804.
- Morley, R., D. W. Eccleston, C. P. Douglas, W. E. J. Greville, D. J. Scott, and J. Anderson. 1970. Xylene poisoning: report on one fatal case and two cases of recovery after prolonged unconsciousness. *Br. Med. J.* 3:442-443.
- Morvai, V., A. Hudák, Gy. Ungváry, and B. Varga. 1976. ECG changes in benzene, toluene and xylene poisoned rats. *Acta Med. Acad. Sci. Hung.* 33:275-286.
- Moses, R. E., and C. C. Richardson. 1970. Replication and repair of DNA in cells of Escherichia coli treated with toluene. *Nat. Acad. Sci. U.S.A.* 67:674-681.
- Moss, A. H., P. A. Gabow, W. D. Kaehny, S. I. Goodman, and L. A. Haut. 1980. Fanconi's syndrome and distal renal tubular acidosis after glue sniffing. *Ann. Intern. Med.* 92:69-70.
- Nelson, K. W., J. F. Ege, Jr., M. Ross, L. E. Woodman, and L. A. Wood. 1943. Sensory response to certain industrial solvent vapors. *J. Ind. Hyg. Toxicol.* 25:282-285.

- Nicholson, W. J., I. J. Selikoff, and H. Seidman. 1978. Mortality experience of styrene-polystyrene polymerization workers. *Scand. J. Work Environ. Health* 4(Suppl. 2):247-252.
- Nomiyama, K., and H. Nomiyama. 1978. Three fatal cases of thinner-sniffing, and experimental exposure to toluene in human and animals. *Int. Arch. Occup. Environ. Health* 41:55-64.
- O'Brien, E. T., W. B. Yeoman, and J. A. E. Hobby. 1971. Hepatorenal damage from toluene in a "glue sniffer." *Br. Med. J.* 2:29-30.
- Ogata, M., K. Tomokuni, and Y. Takatsuka. 1970. Urinary excretion of hippuric acid and m-or p-methylhippuric acid in the urine of persons exposed to vapours of toluene and m- or p-xylene as a test of exposure. *Br. J. Ind. Med.* 27:43-50.
- Overton, E. 1899. Ueber die allgemeinen osmotischen Eigenschaften der Zelle, ihre vermutlichen Ursachen und ihre Bedeutung für die Physiologie. *Vierteljahrsschr. Naturforsch. Ges. Zuerich* 44:88-135.
- Parmeggiani, L., and C. Sassi. 1954. Sul rischio professionale da toluolo: Indagini ambientali e ricerche cliniche nella intossicazione cronica. (Occupational hazards from toluene: Atmospheric investigations and clinical findings in chronic poisoning). *Med. Lav.* 45:574-583. [Current List of Medical Literature 28:20244, 1955.]
- Peterson, R. G., and J. V. Bruckner. 1976. The development of tolerance to toluene in an animal model for human solvent abuse. *Neurosci. Abs.* 2(Part 2):857 (Abstract 1268).
- Pinkas, J. 1972. Hobby-induced factor VII deficiency. *Haemostasis* 1:52-54.
- Powars, D. 1965. Aplastic anemia secondary to glue sniffing. *N. Engl. J. Med.* 273:700-702.
- Press, E., and A. K. Done. 1967. Solvent sniffing. Physiologic effects and community control measures for intoxication from the intentional inhalation of organic solvents. I and II. *Pediatrics* 39:451-462; 611-622.
- Reisin, E., A. Teicher, R. Jaffe, and H. E. Eliahou. 1975. Myoglobinuria and renal failure in toluene poisoning. *Br. J. Ind. Med.* 32:163-168.

- Reynolds, E. S. 1972. Comparison of early injury to liver endoplasmic reticulum by halomethanes, hexachloroethane, benzene, toluene, bromobenzene, ethionine, thioacetamide and dimethylnitrosamine. *Biochem. Pharmacol.* 21:2555-2561.
- Reynolds, E. S., and A. G. Yee. 1968. Liver parenchymal cell injury. VI. Significance of early glucose-6-phosphatase suppression and transient calcium influx following poisoning. *Lab. Invest.* 19: 273-281.
- Rhudy, R. L., D. C. Lindberg, J. W. Goode, D. J. Sullivan, and E. J. Gralla. 1978. Ninety-day subacute inhalation study with toluene in albino rats. *Toxicol. Appl. Pharmacol.* 45:284-285 (Abstract 150).
- Rigdon, R. H. 1949. Effect of antihistamine on the localization of trypan blue in xylene treated areas of skin. *Proc. Soc. Exp. Biol. Med.* 71:637-639.
- Salmona, M., J. Pachecka, L. Cantoni, G. Belvedere, E. Mussini, and S. Garattini. 1976. Microsomal styrene mono-oxygenase and styrene epoxide hydase activities in rats. *Xenobiotica* 6:585-591.
- Sasa, M., S. Igarashi, T. Miyazaki, K. Miyazaki, S. Nakano, and I. Matsuoka. 1978. Equilibrium disorders with diffuse brain atrophy in long-term toluene sniffing. *Arch. Otorhinolaryngol.* 221:163-169.
- Satran, R., and V. N. Dodson. 1963. Toluene habituation. Report of a case. *N. Engl. J. Med.* 268:719-721.
- Savolainen, H. 1978. Distribution and nervous system binding of intraperitoneally injected toluene. *Acta Pharmacol. Toxicol.* 43:78-80.
- Savolainen, H., P. Pfäffli, M. Helojoki, and M. Tengén. 1979a. Neurochemical and behavioural effects of long-term intermittent inhalation of xylene vapour and simultaneous ethanol intake. *Acta Pharmacol. Toxicol.* 44:200-207.
- Savolainen, K., V. Riihimäki, and M. Linnoila. 1979b. Effects of short-term xylene exposure on psychophysiological functions in man. *Int. Arch. Occup. Environ. Health* 44:201-211.
- Savolainen, K., V. Riihimäki, A. M. Seppäläinen, and M. Linnoila. 1980. Effects of short-term m-xylene exposure and physical exercise on the central nervous system. *Int. Arch. Occup. Environ. Health* 45:105-121.

- Schenkman, J. B., D. L. Cinti, and P. Moldeus. 1973. The mitochondrial role in hepatic cell mixed-function oxidation. *Ann. N.Y. Acad. Sci.* 212:420-427.
- Schmid, E. 1956. Die Augenhornhauterkrankung der Möbelpolierer (Diseases of the cornea in furniture polishers.) *Arch. Gewerbepathol. Gewerbehyg.* 15:37-44. [Current List of Medical Literature 31:28688, 1957.]
- Seppäläinen, A. M., K. Husman, and C. Mårtensson. 1978. Neurophysiological effects of long-term exposure to a mixture of organic solvents. *Scand. J. Work Environ. Health* 4:304-314.
- Shigeta, S., H. Aikawa, T. Misawa, and A. Kondo. 1978. Effect of single exposure to toluene in Sidman avoidance response in rats. *J. Toxicol. Sci.* 3:305-312.
- Shirabe, T., T. Tsuda, A. Terao, and S. Araki. 1974. Toxic polyneuropathy due to glue-sniffing. Report of two cases with a light and electron-microscopic study of the peripheral nerves and muscles. *J. Neurol. Sci.* 21:101-113.
- Simmon, V. F., and K. Kauhanen. 1978. In Vitro Microbiological Mutagenicity Assays of Isopropyl Benzene (Cumene). Final report. Prepared for U.S. Environmental Protection Agency, Water Supply Research Laboratory, Cincinnati, Ohio. Contract No. 68-03-11-74. SRI project LSU-5612. Stanford Research Institute International, Menlo Park, Calif. 18 pp.
- Smolik, R., K. Grzybek-Hryniewicz, A. Lange, and W. Zatoński. 1973. Serum complement level in workers exposed to benzene, toluene and xylene. *Int. Arch. Arbeitsmed.* 31:243-247.
- Smyth, H. F., and H. F. Smyth, Jr. 1928. Inhalation experiments with certain lacquer solvents. *J. Ind. Hyg.* 10:261-271.
- Smyth, H. F., Jr., C. P. Carpenter, C. S. Weil, U. C. Pozzani, and J. A. Striegel. 1962. Range-finding toxicity data: List VI. *Am. Ind. Hyg. Assn. J.* 23:95-107.
- Society of the Plastics Industry, Inc. 1979. Investigation of Workers Exposed to Styrene in the Reinforced Plastics Industry. Report of a study conducted by the University of Cincinnati under contract to The Society of the Plastics Industry, Inc., New York.
- Spiro, R., M. Van Ert, J. F. Gamble, P. Wolf, and A. J. McMichael. 1976. Toxicologic, industrial hygiene and epidemiologic considerations in the possible association between SBR manufacturing and

- neoplasms of lymphatic and hematopoietic tissues. Pp. 67-112 in L. Ede, ed. Proceedings of NIOSH Styrene-Butadiene Briefing, Covington, Ky., April 30, 1976. HEW Publication No. (NIOSH) 77-129. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio.
- Stern, F., and J. Oser. 1979. Mortality and industrial hygiene study of workers exposed to toluene. Tox-Tips No. 37:37.
- Sterner, J. H. 1941. Study of hazards in spray painting with gasoline as a diluent. J. Ind. Hyg. Toxicol. 23:437-448.
- Stocké, A. 1929. Akute Xylol- und Toluolvergiftungen beim Tiefdruckverfahren. (Acute xylene and toluene poisoning in the intaglio printing industry). Zentralbl. Gewerbehyg. Unfallverhuet. 16:355-359.
- Suhr, E. 1975. Comparative investigation of the state of health of gravure printers exposed to toluene. Gesellschaft zur Förderung des Tiefdrucks e. V., Wiesbaden, Federal Republic of Germany. [92] pp.
- Sukhanova, V. A., L. M. Makar'eva, and V. I. Boiko. 1969. Investigation of functional properties of leukocytes of workers engaged in manufacture of xylene. Hyg. Sanit. (USSR) 34(9): 448-450.
- Sullivan, C. W., and B. E. Volcani. 1976. Role of silicon in diatom metabolism. VII. Silicic-acid-stimulated DNA synthesis in toluene-permeabilized cells of Cylindrotheca fusiformis. Exp. Cell Res. 98:23-30.
- Suzuki, T., S. Shimbo, and H. Nishitani. 1974. Muscular atrophy due to glue sniffing. Int. Arch. Arbeitsmed. 33:115-123.
- Svirbely, J. L., R. C. Dunn, and W. F. von Oettingen. 1943. The acute toxicity of vapors of certain solvents containing appreciable amounts of benzene and toluene. J. Ind. Hyg. Toxicol. 25:366-373.
- Syrovadko, O. N. 1977. (English summary) Working conditions and health status of women handling organosiliceous varnishes containing toluene. Gig. Tr. Prof. Zabol. No. 12:15-19.
- Taher, S. M., R. J. Anderson, R. McCartney, M. M. Popovtzer, and R. W. Schrier. 1974. Renal tubular acidosis associated with toluene "sniffing." N. Engl. J. Med. 290:765-768.

- Tähti, H., J. Ruuska, and H. Vapaatalo. 1977. Toluene toxicity studies on rats after one week inhalation exposure. *Acta Pharmacol. Toxicol.* 41(Suppl. IV):78.
- Takeuchi, Y. 1969. Experimental studies on the toluene poisoning--chiefly on the findings of peripheral blood and adrenal gland. *Ind. Health* 7:31-45.
- Takeuchi, Y., and N. Hisanaga. 1977. The neurotoxicity of toluene: EEG changes in rats exposed to various concentrations. *Br. J. Ind. Med.* 34:314-324.
- Taulbee, J., D. Andjelkovic, T. Williams, J. F. Gamble, and P. Wolf. 1976. A study of possible associations between exposure to SBR processes and mortality from leukemia and related diseases based on toxicologic, industrial hygiene and epidemiologic considerations (for workers in the 1951 and 1964 cohorts and deaths 1964-1973). Pp. 113-162 in L. Ede, ed. *Proceedings of NIOSH Styrene-Butadiene Briefing*, Covington, Ky., April 30, 1976. HEW Publication No. (NIOSH) 77-129. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio.
- Taylor, G. J., and W. S. Harris. 1970. Glue sniffing causes heart block in mice. *Science* 170:866-868.
- Towfighi, J., N. K. Gonatas, D. Pleasure, H. S. Cooper, and L. McCree. 1976. Glue sniffer's neuropathy. *Neurology* 26:238-243.
- Ungváry, G., A. Hudák, Z. Bors, and G. Folly. 1976. The effect of toluene on the liver assayed by quantitative morphological methods. *Exp. Mol. Pathol.* 25:49-59.
- U.S. Environmental Protection Agency. 1979. Toluene: Ambient Water Quality Criteria. Criteria and Standards Division, Office of Water Planning and Standards, U.S. Environmental Protection Agency, Washington, D.C.
- U.S. National Institute for Occupational Safety and Health. 1973. Criteria for a Recommended Standard... Occupational Exposure to Toluene. Publication No. HSM 73-11023. (Available from the National Technical Information Service, Springfield, Va., as PB-222 219.) U.S. Department of Health, Education, and Welfare, Public Health Service, National Institute for Occupational Safety and Health, Cincinnati, Ohio. 98 pp.
- U.S. National Institute for Occupational Safety and Health. 1975. Criteria for a Recommended Standard... Occupational Exposure to Xylene. HEW Publication No. (NIOSH) 77-168. U.S. Department of Health, Education, and Welfare, Public Health Service,

- Valette, G., and R. Carvier. 1954. Absorption percutanee et constitution chimique. Cas des hydrocarbures, des alcools et des esters. Arch. Int. Pharmacodyn. 97:232-240.
- von Oettingen, W. F., P. A. Neal, and D. D. Donahue. 1942a. The toxicity and potential dangers of toluene; Preliminary report. J. Am. Med. Assoc. 118:579-584.
- von Oettingen, W. F., P. A. Neal, D. D. Donahue, J. L. Svirebely, H. D. Baernstein, A. R. Monaco, P. J. Valaer, and J. L. Mitchell. 1942b. The toxicity and potential dangers of toluene, with special reference to its maximal permissible concentration. U.S. Public Health Bulletin No. 279. U.S. Government Printing Office, Washington, D.C. 50 pp.
- Watson, J. M. 1977. 'Glue-sniffing' in profile. Practitioner 218:255-259.
- Weisenberger, B. L. 1977. Toluene habituation. J. Occup. Med. 19:569-570.
- Werner, H. W., R. C. Dunn, and W. F. von Oettingen. 1944. The acute effects of cumene vapors in mice. J. Ind. Hyg. Toxicol. 26:264-266.
- Wilson, R. H. 1943. Toluene poisoning. J. Am. Med. Assoc. 123:1106-1108.
- Wolf, M. A., V. K. Rowe, D. D. McCollister, R. L. Hollingsworth, and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Experiments on laboratory animals. AMA Arch. Ind. Health 14:387-398.
- Wyse, D. G. 1973. Deliberate inhalation of volatile hydrocarbons: A review. Can. Med. Assoc. J. 108:71-74.
- Yager, J. W. 1973. Congenital malformations and environmental influence: The occupational environment of laboratory workers. J. Occup. Med. 15:724-728.
- Yushkevich, L. B., and M. V. Malysheva. 1975. Study of the bone marrow as an index of experimentally-induced poisoning with chemical substances (such as benzene and its homologs). Sanit. Toksikol. Metody Issled. Gig:36-41. [Chem. Abs. 87:112626m, 1977.]
- Zimmerman, S. W., K. Groehler, and E. J. Beirne. 1975. Hydrocarbon exposure and chronic glomerulonephritis. Lancet 2:199-201.

BIOLOGICAL EFFECTS IN MAMMALS: STYRENE AND STYRENE OXIDE

Unlike toluene, the xylenes, ethylbenzene, and cumene, which occur naturally, styrene and its oxide are produced synthetically. The extensive use of styrene in the manufacture of plastics and in the rubber industry has drawn attention to its potential effects on health. Therefore, in contrast to the compounds covered in Chapter 6, there are considerable data on the biological effects of styrene and its oxide, which is often a by-product in the manufacture of styrene.

This chapter contains a discussion of the toxicity, carcinogenicity, mutagenicity, and teratogenicity of styrene and styrene oxide. Studies of human populations exposed to these compounds are discussed under Epidemiological Studies, towards the end of the section on styrene.

STYRENE

Styrene is primarily a narcotic and an irritant of the skin and mucous membranes. It may be absorbed into the bloodstream via all routes, including peroral administration or inhalation, percutaneous absorption, or after subcutaneous or intraperitoneal administration. In occupational settings, the pulmonary or percutaneous routes are most common (Leibman, 1975; Proctor and Hughes, 1978).

Acute Exposure to Styrene

Acute exposure to high concentrations of styrene may produce irritation of the mucous membranes of the upper respiratory tract, nose, and mouth, followed by symptoms of narcosis, muscular contraction, and death due to respiratory center paralysis (Key et al., 1977).

Spencer et al. (1942) reported that rats and guinea pigs inhaling concentrations of styrene ranging from 1,300 to 10,000 ppm experienced increased eye and nose irritation with increased concentrations. General weakness and unsteadiness were observed after 12 to 30 hr of exposure to 1,300 ppm. Exposure to 2,500 ppm resulted in weakness, stupor, lack of coordination, loss of equilibrium, tremors, and unconsciousness after 10 to 12 hr. All rats and guinea pigs died within 21 and 14 hr, respectively. At 5,000 ppm, there were immediate effects on the central nervous system and the animals became unconscious within 1 hr. At exposures of 10,000 ppm, all animals died within 3 hr. Between 2 and 4 weeks after exposure, the surviving animals were autopsied. The most prominent organ lesions,

which were found in the lungs, were characterized by congestive hemorrhage, and edema. There were also some parenchymatous changes in the liver and kidneys.

Wolf et al. (1956) determined the oral LD₅₀ of styrene in rats to be 5 g/kg body weight. Comparisons indicated that styrene was more acutely toxic than benzene (LD₅₀, 5.6 g/kg) and toluene (LD₅₀, 7.0 g/kg), but less toxic than xylene (LD₅₀, 4.3 g/kg). In these studies, no confidence limits were supplied. Thus, it is difficult to compare the relative toxicity of these compounds. When the rats were autopsied, the investigators noted slight changes in the liver and kidneys.

The acute toxic levels of styrene for different species are presented in Table 7-1. Its acute toxicity appears to be unrelated to its biotransformation, but is similar to that of other hydrocarbons such as toluene, xylenes, and ethylbenzene (Leibman, 1975). The urinary metabolites of styrene are all less toxic than styrene.

Ohtsuji and Ikeda (1971) reported that the pretreatment of rats with phenobarbital enhanced selectively the metabolism of styrene to styrene oxide. Administration of 2-diethylaminoethyl diphenylvalerate hydrochloride (SKF 525-A) depressed the metabolism of styrene.

Hepatic effects and metabolism have also been studied by a number of investigators. Increased serum alanine aminotransferase activity and histological examination indicated that styrene in intraperitoneal doses of 2-3 g/kg body weight caused hepatic necrosis in hamsters. The acute lethality was increased by pretreatment with phenobarbital (Parkki et al., 1978).

Based on observations that glutathione inhibits the covalent binding of styrene in vitro, Parkki (1978) has proposed that glutathione plays a role in the acute toxicity of styrene. Administration of styrene to hamsters in a dose of 1 g/kg body weight for 7 days was not sufficient to cause hepatotoxic effects. However, the administration of diethylmaleate (a depleter of reduced glutathione) with styrene (~ 600 mg/kg) resulted in liver damage, suggesting that glutathione protects the liver during longer exposure to styrene. A critical concentration of glutathione, approximately 1 μ mol/g liver wet weight, which is ~1 mmol/lit, was found to prevent styrene toxicity. Cell damage occurred when the concentration of reduced glutathione decreased below this level. But the administration of methionine (a precursor of reduced glutathione) with styrene protected the liver against hepatotoxicity from styrene as indicated by the serum alanine aminotransferase activity.

TABLE 7-1. Acute Toxic Levels of Styrene for Different Species

<u>Species</u>	<u>Route</u>	<u>Toxicity</u>	<u>Dose</u>	<u>Reference</u>
Rat	Oral	LD ₅₀ ^a	5 g/kg	Wolf <u>et al.</u> , 195
	Intraperitoneal	LD ₅₀	2.15-2.86 g/kg	Ohtsuji and Ikeda
	Inhalation	LC ₅₀ ^b	11.8 g/m ³ /4 hr (2,800 ppm)	Shugaev, 1969
	Inhalation	LCLo	5,000 ppm	Spencer <u>et al.</u> ,
Mouse	Oral	LD ₅₀	0.316 g/kg	Christensen <u>et al.</u>
Mouse	Inhalation	LC ₅₀	21.0 g/m ³ /2 hr (5,000 ppm)	Shugaev, 1969
Mouse	Inhalation	LCLo ^c	10,000 ppm	Christensen <u>et al.</u>
Pig	Inhalation	LCLo	12 g/m ³ /14 hr (2,820 ppm)	Spencer <u>et al.</u> ,

^a Lethal dose for 50% kill.

^b Lethal concentration for 50% kill.

^c Lowest published lethal concentration.

Intraperitoneal administration of styrene in doses of 150 to 1,000 mg/kg body weight to mice, rats, hamsters, and guinea pigs caused a depression of the hepatic nonprotein sulfhydryl content. Mice were the most sensitive, and rats the most resistant (Vainio and Makinen, 1977).

Fourteen hours after rats were given single intraperitoneal injections of styrene in doses of 10, 100, or 500 mg/kg body weight, the Michaelis rate constants of benzo(a)pyrene hydroxylase and aldehyde epoxidase of liver microsomes were significantly reduced. The catalytic properties of styrene oxide synthetase were not modified (Lambotte-Vandepaer et al., 1978).

Subchronic and Chronic Exposures to Styrene

A 2-year bioassay to test the carcinogenicity of styrene was conducted using Fischer 344 rats and B6C3F1 mice (U.S. Department of Health, Education, and Welfare, 1979). Styrene in combination with corn oil was administered by gavage to groups of 50 male and 50 female animals of each species. Forty rats of each sex and 20 mice of each sex were fed corn oil and served as the controls. Groups of rats were fed 2,000 and 1,000 mg/kg of styrene for 78 weeks and observed for 27 weeks. Another group of rats was given 500 mg/kg for 103 weeks and observed for 1 week. Groups of mice were given 300 and 150 mg/kg of styrene for 78 weeks and observed for 13 weeks following the completion of the test period.

In order to establish dose levels for chronic studies, subchronic toxicity tests were conducted with both Fischer 344 rats and B6C3F1 mice (U.S. Department of Health, Education, and Welfare, 1979). Animals were given styrene mixed with corn oil via intubation 5 days/week for 7 weeks, followed by a 1-week observation period. The survival rates of these animals are shown in Table 7. Aside from a slight depression in weight gain relative to controls, there were no observed clinical abnormalities in the treated mice that could be attributed to the administration of styrene.

In the study of chronic exposure, 6-week-old male and female Fischer 344 rats were intubated with styrene at levels of 2,000 mg/kg and 1,000 mg/kg for 78 weeks, followed by an observation period of 27 weeks (U.S. Department of Health, Education, and Welfare, 1979). Due to excessive mortality through the first 22 weeks in the animals receiving 2,000 mg/kg, additional groups of animals receiving 500 mg/kg were placed on test. In the same study, 6-week-old male and female B6C3F1 mice were intubated with styrene at levels of 300 mg/kg and 150 mg/kg for 78 weeks, followed by a 13-week observation period.

TABLE 7-2. Survival Rate of Rats and Mice Given Styrene Mixed in Corn Oil 5 Days/Week for 7 Weeks^a

<u>Rats</u>			<u>Mice</u>		
<u>Dose, mg/kg</u>	<u>Males</u>	<u>Females</u>	<u>Dose, mg/kg</u>	<u>Males</u>	<u>Female</u>
3,160	3/5	4/5	681	1/5	1/5
2,150	5/5	4/5	464	4/5	5/5
1,470	5/5	4/5	316	5/5	4/5
1,000	4/5	5/5	215	4/5	5/5
681	5/5	5/5	147	5/5	5/5
0	5/5	5/5	0	5/5	5/5

^aData from U.S. Department of Health, Education, and Welfare, 1979.

Dose-related depression of mean body weight was apparent in male rats, but not in the females. Only the weights of the females receiving 1,000 mg/kg were less than those of the controls. No other clinical signs were reported. The rats receiving 2,000 mg/kg were the only ones to show statistically significant poorer survival than their controls.

Inflammatory, degenerative, and proliferative lesions were found to be common in aged Fischer 344 rats. The investigators suggested that hepatic necrosis, which was observed in several of the high dose rats, may have contributed to the high mortality.

Slight dose-related depression of mean body weight was observed among female mice but not among males. No other clinical signs were noted. Although there was a significant association between dosage and mortality in male mice (Table 7-2), adequate numbers of male mice were at risk from late-developing tumors.

A variety of the inflammatory and proliferative lesions commonly seen in B6C3F1 mice occurred with approximately equal frequency in treated and control mice of both sexes. Except for tumors of the lung in treated male mice, observed neoplastic lesions were apparently not related to administration of the compound.

There was a statistically significant positive association between styrene dosage and the incidences of a combination of adenomas and carcinomas of the lung in male mice. However, the investigators concluded that the results did not permit a firm conclusion regarding carcinogenicity due to the variation of the incidence of these neoplasms in control male mice in earlier studies conducted at the same laboratory. When styrene-treated groups were compared to vehicle controls, there were no significant increases in tumor incidence at any other site in male mice, at any site in female mice, or in rats of either sex. Although the incidence of neoplasms was significantly higher in male B6C3F1 mice, the investigators concluded that, under the conditions of the study, there was no "convincing" evidence of carcinogenicity in Fischer 344 rats or B6C3F1 mice.

Although the carcinogenesis bioassay for styrene was inconclusive it is clear that styrene can produce hepatotoxicity. The data allow some speculation on the mechanism by which styrene produces its hepatotoxicity.

These data suggest that styrene is metabolized by the mixed-function oxidase enzyme system. It is likely that this process produces a metabolite that can cause hepatotoxicity. The reduction of sulphydryl levels in liver and conjugation of reduced glutathione

(GSH) suggest that a metabolite of styrene can probably bind covalently to liver protein in a manner similar to metabolites of bromobenzene and acetaminophen, which are two well known hepatotoxins. Thus, styrene may cause hepatotoxicity by mechanisms similar to those of other known hepatotoxins.

Neurotoxicity

The current occupational threshold limit value for styrene of 100 ppm, which was set by the American Conference of Governmental Industrial Hygienists (1978), is based chiefly on a few studies involving short-term exposures of human subjects (Carpenter et al., 1944; Stewart et al., 1968). However, the neurotoxic effects of styrene have been studied more intensively during the past 10 years, particularly by Scandinavian workers. These recent reports will certainly require a reevaluation of the threshold limit value for styrene.

Experimental Exposures of Humans. Carpenter et al. (1944) exposed humans in an exposure chamber to 800 ppm of styrene vapor for 4 to 8 hr. They found that styrene caused immediate eye and nose irritation, a persistent metallic taste, drowsiness, unsteadiness, and loss of equilibrium. In addition, after the termination of exposure, slight muscular weakness and depression occurred.

Stewart et al. (1968) found no significant objective or subjective effects on subjects exposed to approximately 50, 100, or 200 ppm styrene for 1 hr. However, exposure to 375 ppm produced definite impairments of balance, manual dexterity, and muscular coordination as well as complaints of headache, nausea, and eye irritation. Exposure for 7 hr to approximately 100 ppm produced mild eye and throat irritation in three of six subjects, and three of them reported some difficulty in performing a test of balance (modified Romberg test).

Gamberale and Hultengren (1974) exposed 12 subjects to 50, 150, 250, and 350 ppm styrene in four continuous 30-min exposures. Performance of subjects on a reaction-time test was impaired at the 350 ppm level, whereas no changes in performance were observed in tests of manual dexterity and perceptual speed.

Occupational Exposures. Wilson (1944) found that workers exposed to styrene concentration of 500 ppm or less complained of eye, nose, and lung irritation and of feelings of lassitude and fatigue. Götell et al. (1972), in a study of 17 men occupationally exposed to styrene, found no abnormalities in tendon reflexes or

other neurological tests, although there were many complaints of eye, nose, and throat irritation. The simple reaction time of workers exposed to mean styrene levels of 150 ppm or greater was significantly greater than it was for workers exposed to lower concentrations.

Dolmierski et al. (1976) examined the electroencephalograms of two groups of styrene workers, one that had been employed for an average of 1 year and the other for 10 years. In the former group, 31 of 43 persons had abnormal electroencephalograms and other signs and symptoms indicating involvement of the central nervous system. In the group that had been employed for an average of 10 years, only 4 of 18 workers had abnormal electroencephalograms. The difference between these two groups of workers was attributed to the fact that workers whose health is affected in a particular occupation will generally resign sooner than those less affected. Abnormal electroencephalograms had previously been reported in styrene workers by Klinková-Deutschová (1962) and Roth and Klinková-Deutschová (1963).

The most extensive series of neuropsychological studies of exposure to styrene was conducted on 98 Finnish workers. These workers had been exposed from 0.5 to 14 years (mean = 4.9). Urinary mandelic acid concentrations were used as a measure of current average exposure to styrene. Intelligence, memory, visuomotor speed, visuomotor accuracy, vigilance, and psychomotor performance were measured in the styrene workers and in 43 control subjects (Lindström et al., 1976). The only significant differences between styrene-exposed and control subjects were observed in the results of the tests of visuomotor accuracy and psychomotor performance. The changes in visuomotor accuracy occurred when urinary mandelic acid was present at a mean level of 800 mg/liter, which corresponds to a time-weighted average styrene exposure of approximately 35 ppm (Härkönen et al., 1978). More pronounced impairments in both visuomotor accuracy and in psychomotor performance occurred at average mandelic acid concentrations of 1,200 mg/liter or more (styrene exposure of 55 ppm).

The results of the psychological tests were not correlated with consumption of alcohol by the styrene workers (Lindstrom et al., 1978). One-third of the workers having urinary mandelic acid concentration exceeding 700 mg/liter (approximately 30 ppm or a time-weighted average styrene exposure) had abnormal electroencephalograms. Maximum motor conduction velocities of the median, ulnar, peroneal, and posterior tibial nerves, the conduction velocities of slow fibers of the ulnar and peroneal nerves, and the sensory conduction velocities of the ulnar and median nerves were unaffected (Seppäläinen and Härkönen, 1976). In a survey of subjective symptoms, the investi-

gators learned that the styrene workers had significantly more complaints of fatigue, difficulties in concentration, irritability, dizziness, and nausea than did the control subjects. However, there was no significant correlation between the frequency of these symptoms and the level of exposure. Furthermore, the symptoms of those workers who had previously been found to have abnormal electroencephalograms or impaired performance on psychological tests were not significantly different from those of other styrene workers (Härkönen, 1977).

Rosén et al. (1978) examined electroencephalograms and peripheral nerve conduction velocities in 33 workers exposed to styrene. Some of the workers had been exposed to concentrations above 50 ppm (range 74-175 ppm; mean, 125 ppm), some at approximately the Swedish TLV of 50 ppm (range, 21-60 ppm), and some at levels well below 50 ppm (all measurements <5 ppm). The investigators reported that there were no changes in motor conduction velocities but that there were slower than normal sensory conduction velocities as well as increased amounts of fast activity in electroencephalograms taken from the central and precentral regions. Ten of the workers exposed to styrene had a mild polyneuropathy, which appeared to be related to the duration and magnitude of styrene exposure.

In another study (Lilis et al., 1978; Lorimer et al., 1978), 494 workers exposed to styrene were examined. Prenarcotic symptoms, such as lightheadedness, eye irritation, and irritation of mucous membranes, were significantly more frequent in a "high" exposure group than in a "low" exposure group. A distal hypoesthesia of the legs occurred in 8.5% of the cases. The conduction velocities of both radial and peroneal nerves were less than normal in 18.8% and 16.4% of the workers, respectively. There was consistent decrement in peroneal nerve conduction velocity as the exposure to styrene exposure continued, but no such relationship was observed for radial nerve conduction velocities.

In a study of 152 workers who were occupationally exposed to styrene in concentrations ranging from 1 to 244 ppm, Brooks et al. (1979) found no increased incidence of neurological symptoms such as weakness, nausea, irritability, headache, or lightheadedness. Workers exposed to the higher concentrations of styrene (82 ± 44 ppm) had significantly more complaints of eye, nose, and throat irritation than did those in the lower (15 ± 9 ppm) exposure group. The higher exposures to styrene were also associated with decreases in performance in psychomotor tests of choice reaction time, eye-hand coordination, and digit span. The psychomotor test performance of workers exposed to the higher levels of styrene appeared to deteriorate progressively as exposure continued.

Studies of Animals. Studies of the neurotoxic effects of styrene in animals are rare. General toxicological studies have

shown that acute exposures of rats and guinea pigs to styrene at levels of 2,500 ppm or above can produce loss of equilibrium, tremors, convulsions, and unconsciousness (Spencer et al., 1942). Rats, guinea pigs, rabbits, and monkeys exposed to 1,300 ppm for 7 to 8 hr/day, 5 days/week showed no obvious signs of toxicity in the central nervous system, but guinea pigs did exhibit severe irritation of the lungs and all of the animals experienced eye and nose irritation (Spencer et al., 1942). Exposures to 1,300 ppm styrene for 7 - 8 hr/day, 5 days/week for 1 year produced no obvious toxic effects in rabbits and monkeys (Wolf et al., 1956).

There were slight changes in the composition of brain protein and increased proteolysis in male rats exposed to 300 ppm styrene for 6 hr/day, 5 days/week for 2 to 11 weeks (Savolainen and Pfaffli, 1977, 1978). Under the same exposure conditions, Seppäläinen (1978) measured the conduction velocity of the caudal nerve in the rat tail. She observed a small decrease in conduction velocity after 6 weeks of exposure, but no difference from control rats after 4, 8, or 11 weeks.

Savolainen et al. (1980) observed rats in an open-field test before and after 4, 9, and 13 weeks of exposure to 300 ppm styrene 6 hr/day, 5 days/week. Half of the rats were also given ethanol in their drinking water (at 15% V/V). No differences were seen in measurements of ambulation, rearing, or in frequency or duration of preening in rats exposed to styrene alone. In rats exposed to both styrene and ethanol, some increases in ambulation occurred at 12 weeks and increases in preening time at 4 weeks. Small decreases in glial cell acid proteinase and cerebral RNA were noted in styrene-exposed animals, but within 2 weeks after removing the animals from the exposure there were no differences in these biochemical measurements.

Striking effects on positional and rotatory nystagmus are produced by infusing styrene into rabbits intravenously. Larsby et al. (1978) reported that these changes occurred when levels of styrene in the blood reached 40 ppm, which is approximately 10 times the value expected from inhalation exposures to 100 ppm styrene.

Epidemiological Studies

Taulbee et al. (1976) examined a cohort of workers engaged in the production of styrene-butadiene rubber (SBR) between 1951 and 1964. They analyzed the deaths that occurred in this cohort between 1964 and 1973. "No worker known to have died in the period 1964-1973 due to neoplasm of the lymphatic and hematopoietic tissue spent any time in a job identified as having OTG [Occupational Title Group] Synthetic. However, some workers who died of neoplasms of the lymphatic and hematopoietic tissue did spend time in departments

identified by the company as possibly having involvement in the synthetic operation. From the data available, there may be a very slightly increased (relative) risk of dying due to neoplasms of the lymphatic and hematopoietic tissues from having worked in these departments. The magnitude of this (relative) risk is not large (about 1.5), however." Workers in these departments are still being followed.

Spirtas et al. (1976) conducted a similar case-control study in another rubber manufacturing company. Their results helped strengthen the hypothesis that work experience in a synthetic rubber plant may be associated with neoplasms of the lymphatic and hematopoietic tissues. Furthermore, they demonstrated an even stronger association with a group of lymphomas.

Lorimer et al. (1978) studied a group of 493 styrene production workers. Those exposed to "high" (hundreds of ppm) levels of styrene had histories of significantly frequent prenarcotic symptoms and acute lower respiratory symptoms as well as decreased peroneal nerve conduction velocities, relative lymphocytosis, and elevated γ -glutamyl transpepsidase. There were no real differences in the chest X-rays, airway dysfunction, other hepatic or hematological indices, sputum cytology, radial nerve conduction velocities, or ophthalmological findings. The authors concluded that, "Clinically significant abnormalities were rare."

Nicholson et al. (1978) and Frentzel-Beyme et al. (1978) reported negative results in mortality studies of styrene-polystyrene polymerization workers. The Frentzel-Beyme study also showed no change in mortality with longer exposures.

In another study involving potential exposure to styrene, the University of Cincinnati conducted the first of several surveys sponsored by the reinforced plastics industry to examine the health of its workers. The investigators studied morbidity in 152 workers employed in a reinforced plastics facility that was engaged primarily in the manufacture of boats (Society of the Plastics Industry, Inc., 1979). They examined the workers for both acute and chronic health effects that might be related to their work environment by comparing their health to that of a control population employed at a nearby electronics plant. There was no significant differences between the study and control groups relative to past medical illnesses, irritation of the mucous membrane, or neurologic and respiratory symptoms. Certain findings obtained through psychomotor, behavioral, and pulmonary function testing require further study.

STYRENE OXIDE

Styrene oxide is considerably less volatile and more fat-soluble than benzene. It is more reactive than styrene. Although

experience has not shown styrene oxide to be as hazardous as ethylene oxide, precautions should be taken to prevent excessive pressure under storage or reaction conditions.

The most apparent hazard to health from styrene oxide resides in its ability to cause irritation and sensitization of the skin. In animals, metabolites of styrene oxide are excreted mainly via the kidney. James and White (1967) reported that approximately 80% of a single oral dose was excreted in the urine of rabbits.

Acute Exposure to Styrene Oxide

Undiluted styrene oxide may cause relatively severe irritation and pain to the eyes, but it is not apt to cause serious burns with permanent loss of vision. Solutions as dilute as 1% may have some irritating action. Tests with laboratory animals and human subjects indicate that styrene oxide is capable of causing moderate skin irritation and skin sensitization. These effects may result from single or repeated contact with the undiluted compound or solutions as dilute as 1%. Eight intracutaneous injections (three per week on alternate days) of 0.1 ml of the diluted styrene oxide sensitized guinea pigs (Weil et al., 1963). Experience indicates that persons who have become hypersensitive may react severely when in contact with the vapor or the liquid (Hine and Rowe, 1963).

For systemic toxicity, the feeding of single doses to animals indicated that the LD₅₀ for guinea pigs and rats is approximately 2 g/kg body weight. Single 24-hr exposures of rabbit skin indicated an LD₅₀ of 2.83 g/kg body weight. Rats exposed to air saturated with vapors of styrene oxide survived a 2-hr exposure, but three of six died following a 4-hr exposure (Hine and Rowe, 1963). The acute toxic levels of styrene oxide for different species are presented in Table 7-3.

Styrene oxide administered intraperitoneally in one dose of 375 mg/kg body weight caused a significant decrease in the activities of mixed-function oxidases and in the amount of cytochrome P-450 in the rat liver (Parkki et al., 1976). Also, styrene oxide injected intraperitoneally or incubated in vitro binds covalently to microsomes, protein, and nucleic acid fractions of rat liver (Marniemi et al., 1977).

The interaction of styrene oxide with hepatic cytochrome P-450 in vitro and the effects of inhaled styrene oxide on xenobiotic biotransformation in mouse liver and kidney were studied by Vainio and Elovaara (1979). Female mice (strain CB-20) were killed 0.5 hr,

TABLE 7-3. Acute Toxic Levels of Styrene Oxide for Different Species

<u>Species</u>	<u>Route</u>	<u>Toxicity</u>	<u>Dose</u>	<u>Reference</u>
Rat	Oral	LD ₅₀ ^a	4.29 g/kg	Smyth <u>et al.</u> ,
Rat	Oral	LD ₅₀	3.0 g/kg	Weil <u>et al.</u> ,
Rat	Inhalation	LCLo ^b	500 ppm/4 hr	Smyth <u>et al.</u> ,
Rat	Intraperitoneal	LD ₅₀	0.460-0.610 g/kg	Ohtsuji and I
Rabbit	Skin	LD ₅₀	1.060 g/kg	Smyth <u>et al.</u> ,
Rabbit	Skin	LD ₅₀	0.930 g/kg	Weil <u>et al.</u> ,

^aLethal dose for 50% kill.

^bLowest published lethal concentration.

18 hr, and 5 days after inhaling styrene oxide for 6 hr/day for 3 consecutive days at concentrations of 200, 200, and 100 ppm, respectively. Acute intoxication was manifest, both clinically and as a depression of the nonprotein sulfhydryl content of the liver and kidney. During the recovery period of 5 days, a transient rise in microsomal 7-ethoxycoumarine O-deethylase activity in both tissues paralleled changes in cytochrome P-450 content. The activity of microsomal epoxide hydratase (measured with styrene oxide as the substrate) was not affected by the treatment, neither was the uridine diphosphate-glucuronosyltransferase activity. In the presence of hepatic microsomes from phenobarbital-treated mice, styrene oxide produced a characteristic Type I difference spectrum.

Carcinogenicity

The first experimental indication of the carcinogenic potential of styrene oxide was recently reported by C. Maltoni and coworkers (1979). In this study, the compound was administered in an olive oil solution by stomach tube to Sprague-Dawley rats at two dose levels--50 mg/kg and 250 mg/kg. After 52 weeks of treatment with 4 or 5 doses per week, the animals were allowed to live until spontaneous death. The principal target organ was the stomach. Papilloma in-situ carcinomas, and invasive carcinomas of the forestomach were observed in both sexes at the two levels studied, and there was a clear-cut dose-response relationship. The investigators also reported metastatic carcinomas of the liver and multiple tumors in the same animals. On the basis of their observations, they concluded that "styrene oxide appears to be a very potent direct carcinogen."

Neurotoxicity

There are no data concerning the neurotoxicity of styrene oxide.

GENETIC EFFECTS

Styrene and Styrene Oxide

Styrene has recently attracted considerable attention as a potential mutagen and carcinogen. This possibility is attributed to the probable initial biotransformation of styrene to styrene oxide, an electrophilic compound with the ability to react with nucleophilic sites in tissue macromolecules.

Mutagenic Potential. Reports of the mutagenic potential of styrene in Ames assay have been conflicting. Whereas de Meester et al. (1977), Roberfroid et al. (1978), Vainio (1978), Vainio et al.

(1976), and Watabe et al. (1978) reported evidence of mutagenicity by styrene in the Ames assay, Busk (1979) and Milvy and Garro (1976) reported the converse. In contrast, all of these investigators as well as Stoltz and Withey (1977) found that styrene oxide was mutagenic in both TA1535 and TA100 strains of Salmonella. It appears that the oxide is mutagenic regardless of whether a metabolic activating system is used or not.

A structure activity relationship study has been performed using some derivatives of styrene oxide on Salmonella typhimurium (TA 100 strain) (Sugimura et al., 1978). At equal concentrations, p-chlorostyrene oxide was more lethal than p-methyl-, m-chloro-, or unsubstituted styrene oxide. When the survival fraction was 0.8 or more, the mutagenicities of these compounds increased in the following order: m-chlorostyrene oxide = p-chlorostyrene oxide < styrene oxide < p-methylstyrene oxide. The mutagenicities of these compounds depended only on the reactivity of their benzylic site.

Negative results have been reported for a 100 mM concentration of styrene on a forward mutation system of yeast (Schizosaccharomyces pombe, P₁ strain) fortified with mouse liver microsomal fraction and also on Chinese hamster cells (V₇₉ strain) in the absence of a metabolic activation system for concentrations of styrene as high as 17 mM (Loprieno et al., 1976, 1978). However, the investigators reported that styrene oxide was active in both genetic systems. Because the results obtained by these authors from the host-mediated assay using the forward mutation with Saccharomyces cerevisiae diploid strain D4 are inconclusive, the mutagenicity of styrene and styrene oxide cannot be established unequivocally (Loprieno et al., 1976).

Clastogenic Potential. The association between exposure to styrene and mutagenic events has been strengthened by the observation that workers exposed to styrene show an increase in chromosomal aberrations when compared to controls (Fleig and Thiess, 1978; Harkonen, 1978; Meretoja and Vainio, 1979; Meretoja et al., 1977). According to Meretoja et al. (1978a), the high incidence of aberrant lymphocytes in workers (mean, $15.1 \pm 4.8\%$) as compared to referents (mean, $2.0 \pm 1.3\%$) was retained when the same men were reexamined 1 year later (mean, $16.2 \pm 2.9\%$). However, the frequency of sister chromatid exchanges (SCE) was not significantly increased (mean, 5.3 ± 1.0 SCE/cell) in comparison to the referents (mean, 4.4 ± 0.6 SCE/cell). This finding suggests a specific role of styrene or its metabolites in inducing genetic lesions manifesting themselves mainly as chromosomal breaks.

Meretoja and Vainio (1979) examined the chromosomes of workers from three plants manufacturing polyester plastic products to determine if clastogenic effects resulted from exposure to styrene. The incidence of aberrant cells ranged from 11% to 26% in the ex-

posed group and was 3% or less in the unexposed control groups. The frequency of interphase cells with micronuclei or nuclear bridges was also significantly increased. In-vitro experiments with lymphocytes from humans revealed that the cytotoxicity of styrene oxide is stronger than that of styrene. Although 0.008% (v/v) styrene in the culture for the entire period of growth had no effect on the mitotic activity of lymphocytes, the cells were able to withstand the same concentration of styrene oxide only for the last 8 hr of culture or less. Examination of metaphase chromosomes from cultures containing toxic concentrations of styrene or styrene oxide showed that both chemicals possess clastogenic activity. The incidence of cells with chromosome aberrations was 19% in styrene cultures in comparison to 2% in the control experiments. Meretoja and Vainio did not report the mean number of aberrations per cell.

Similar chromosome aberrations could be induced in rat bone-marrow cells (Meretoja et al., 1978b). When rats were exposed by inhalation to 1.3 g/m³ (300 ppm) styrene in air for 2 to 11 weeks for 6 hr/day, 5 days/week, an increase in the frequency of chromosome aberrations in bone-marrow cells (8%-12% in the exposed group, 1%-6% in the controls) was observed between 9 and 11 weeks.

The capability of styrene oxide (250 mg/kg body weight of mouse) to induce chromosome damage in vivo (by intraperitoneal injection) has also been tested in the BALB/c male mouse by examination of bone-marrow cells, by scoring micronuclei in polychromatic erythrocytes, by observation of meiotic chromosomes from treated males, and by the dominant-lethality test (Fabry et al., 1978). Whereas an increase in the yield of chromatid breaks and chromosome aberrations was observed after exposure in vitro, only negative results were obtained in the tests in vivo. These authors concluded that styrene oxide is potentially capable of breaking mammalian chromosomes but that an exposure to an acute dose in vivo does not produce visible damage in somatic cells or in male germ cells.

Inhalation exposure to styrene oxide (25, 50, 75, and 100 ppm) for 2, 4, or 20 days (25 ppm only for 20 days) had no effect on chromosome aberration rates or SCE frequencies (BrdU-labelling performed in vitro) in the bone marrow cells of Chinese hamsters (Norppa et al., 1979). The only positive response in frequency of aberrations was obtained when styrene oxide was injected intraperitoneally in a dose of 500 mg/kg body weight. One animal out of six showed slightly elevated SCE values after receiving this high dose.

Styrene and its metabolite styrene oxide were also tested for their ability to induce sister chromatid exchanges in Chinese hamster ovary (CHO) cells (de Raat, 1978). Styrene oxide appeared

a potent inducer of SCE. Styrene itself did not increase the number of SCE's per metaphase, even in the presence of a metabolic activation system. The author attributes this lack of SCE induction by styrene in the presence of metabolic activation to a very rapid decomposition of styrene oxide (clearly an SCE-inducing compound) and not to styrene not being converted into its oxide.

Norppa et al. (1980) also subjected 3- to 4-month-old male Syrian hamsters to inhalation exposures to 300 ppm styrene. They observed no significant increase in the number of chromosomally damaged cells in the bone marrow of these animals.

The cytogenetic effects of styrene and styrene oxide on human lymphocytes and tip cells of onion roots (Allium cepa) have been investigated by Linnainmaa et al. (1978a,b). They reported that both compounds induced cytogenetic effects at very low concentrations (0.1% v/v or even less) and that the effects were similar in both human lymphocytes of humans (in vitro) and onion cells (in vivo). Characteristically, styrene caused greater chromosome breakage in human lymphocytes. In the onion cells, styrene induced inhibition of mitotic spindle action. Furthermore, the number of micronuclei and chromosome bridges increased in both test systems, especially after treatment with styrene oxide.

TERATOGENICITY

Styrene and Styrene Oxide

Doses of styrene ranging from 46 to 90 mg/kg body weight injected into the yolk sac of fresh, fertile chicken eggs had no embryotoxic effects (McLaughlin et al., 1963, 1964). However, when injected on the fourth day of incubation, there was an LD₅₀ of 40 µmol/embryo, and malformations were found in up to 20% of treated embryos, depending on the dose and time of injection, but never in the controls (Vainio et al., 1979). In the same study, injections of styrene oxide also caused malformations in developing chicks at concentrations of 0.5-5 µmol/egg. The LD₅₀ for embryos was 1.5 µmol of styrene oxide per egg when injected on the fourth day of incubation.

The synergistic effects of trichloropropylene oxide (1,2-epoxy-2,2,2-trichloropropane) on the embryotoxicity and teratogenicity of styrene and styrene oxide in chick embryos were also investigated recently by Kankaanpää et al. (1979). They injected a total volume of 10 µl each of styrene and styrene oxide into the air space of two eggs on the third day of incubation. Both compounds were found to induce malformations. In the styrene-treated eggs, malformation was observed in 15%, compared to 20% of the styrene-oxide-

treated eggs, and 4.9% in controls. Two more groups of eggs were treated with styrene or styrene oxide administered with trichloropropylene oxide. Malformations in these groups were 33% and 27%, respectively, as compared to 11% in the control group treated with trichloropropylene oxide alone. Thus, at the doses examined, both styrene and styrene oxide are more teratogenic than trichloropropylene oxide.

Doses of 1.5 to 5 mg/m³ of styrene inhaled by rats during entire periods of pregnancy had an embryotoxic effect (Ragule, 1974). In another study, Murray *et al.* (personal communication) evaluated the effect of inhaled styrene monomer on embryonal and fetal development in rats and rabbits. Pregnant Sprague-Dawley rats and New Zealand rabbits were exposed for 7 hr/day to 0, 300, or 600 ppm of styrene on days 6 through 15 (rats) and 6 through 18 (rabbits) of gestation. Styrene was neither embryotoxic nor fetotoxic in rats or rabbits inhaling 300 or 600 ppm of styrene. Some maternal effects (decreased weight gain, decreased food consumption, and increased water consumption) were observed in rats at both levels of exposure, but not in rabbits. No evidence of teratogenicity was detected in either species inhaling concentrations of up to 600 ppm of styrene.

GENERAL SUMMARY

Acute and Chronic Toxicity

Styrene. Styrene liquid and vapor are irritating to the eyes, nose, throat, and skin. Acute exposure to high concentrations of styrene may produce irritation of the mucous membranes of the upper respiratory tract, nose, and mouth, followed by symptoms of narcosis and muscular contractions due to respiratory center paralysis. Styrene (rat oral LD₅₀, 5.0 g/kg body weight) is more acutely toxic than benzene (LD₅₀, 5.6 g/kg body weight) and toluene (LD₅₀, 7.0 g/kg body weight) but less toxic than xylene (LD₅₀, 4.3 g/kg body weight). The acute toxicity of styrene appears to be similar to that of other aromatic hydrocarbons such as toluene, xylenes, and ethylbenzene. The urinary metabolites of styrene are all less toxic than styrene, and therefore may not contribute to its acute toxicity. Pretreatment of rats with phenobarbital enhances selectively the metabolism of styrene to styrene oxide, whereas the administration of 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride (SKF 525-A) depresses the metabolism. These effects may play a vital role in altering the toxicity of styrene as well as in converting the compound to a more toxic and mutagenic product, namely styrene oxide. Reduced glutathione in the liver plays a central role in the development of cell damage by styrene.

Styrene Oxide. The most apparent hazard to health from styrene resides in its ability to cause skin irritation and skin hyper-tization. The effects may result from single or repeated contacts undiluted material and solutions as dilute as 1%. A comparison of oral LD₅₀'s obtained from inhalation and intraperitoneal doses of styrene oxide compared with those of styrene indicates that styrene oxide is 1.5 to 5 times more toxic than styrene. A comparison of the kinetic parameters of styrene oxide in interactions with uninduced microsomes and those induced by phenobarbital and 3-methylcholanthrene in mouse liver and kidney indicates that the binding of styrene oxide is catalyzed by more than one type of P-450 hemoprotein, but predominantly by phenobarbital-induced cytochrome P-450.

toxicity

Objective evidence of the toxicity of styrene to the central nervous system in animals has not been found to result from exposures of 10 ppm or less. Experimental and occupational exposures of humans have shown that eye, nose, and throat irritation occur at levels of 100 ppm or more and that subtle changes in psychological test performance, electroencephalograms, and peripheral nerve conduction result from chronic exposure to levels of 50 ppm or less. There is no data on the neurotoxicity of styrene oxide.

Epidemiological Studies

Epidemiological studies offer few data and are inconclusive. Studies of exposure to styrene indicate that exposure to high concentrations is associated with pre-narcotic symptoms and an increase in the number of symptoms in the lower respiratory tract; however, the authors did not believe that these were clinically significant. A study of plastics workers was generally negative, suggesting a need for further psychomotor, behavioral, and pulmonary function testing. Two mortality studies of workers in the styrene-polystyrene industry were negative.

Genetic Effects

Results in the literature regarding the mutagenicity of styrene oxide in the Ames Salmonella/microsome assay are contradictory. In contrast, styrene oxide has been found to cause mutation with or without the presence of rat liver microsome (i.e., with or without metabolic activation) in histidine-requiring Salmonella strains TA100 and TA1535 (mutable to prototrophy by base-pair substitutions). Styrene oxide is also found to be mutagenic in the yeast system, but results from

the host-mediated assay were inconclusive. Both styrene and styrene oxide have been reported to have clastogenic activity.

Teratogenicity

Styrene was found to be less embryotoxic than styrene oxide. Both compounds cause malformations in developing chicks. Trichloropropylene oxide (1,2-epoxy-3,3,3-trichloropropane), an inhibitor of epoxide hydratase, has some synergistic effect on the embryotoxicity of styrene and styrene oxide.

Carcinogenicity

The only bioassay conducted thus far for styrene is inconclusive. The most significant aspect of the toxicology of styrene oxide is its carcinogenicity. It is of interest that this compound is also a substrate for the mixed-function oxidase enzyme system. Thus, it may be questioned whether styrene oxide itself is a reactive metabolite leading to a carcinogenesis or whether it must be further converted to the ultimate carcinogen.

REFERENCES

- American Conference of Governmental Industrial Hygienists. 1978. TLVs®: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1978. American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio. 94 pp.
- Brooks, S. M., E. A. Emmett, J. Y. Tsay, R. Buncher, L. A. Anderson, V. Elia, and A. Carson. 1979. Epidemiologic study of styrene workers. II. Health and psychomotor status of workers exposed to styrene in reinforced plastics industry. Pp. 185-190 in Annual Report, Department of Environmental Health, Contract USPHS ES 00159. University of Cincinnati, Cincinnati, Ohio.
- Busk, L. 1979. Mutagenic effects of styrene and styrene oxide. *Mutat. Res.* 67:201-208.
- Carpenter, C. P., C. B. Shaffer, C. S. Weil, and H. F. Smyth. 1944. Studies on the inhalation of 1:3-butadiene; with a comparison of its narcotic effect with benzol, toluol, and styrene, and a note on the elimination of styrene by the human. *J. Ind. Hyg. Toxicol.* 26(3):69-78.
- Christensen, H. E., and E. J. Fairchild, eds. 1976. Suspected Carcinogens, 2nd edition. A Subfile of the NIOSH Registry of Toxic Effects of Chemical Substances. HEW Publication No. (NIOSH) 77-149. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio. 251 pp.
- de Meester, C., F. Poncelet, M. Roberfroid, J. Rondelet, and M. Mercier. 1977. Mutagenicity of styrene and styrene oxide. *Mutat. Res.* 56:147-152.
- de Raat, W. K. 1978. Induction of sister chromatid exchanges by styrene and its presumed metabolite styrene oxide in the presence of rat liver homogenate. *Chem. Biol. Interactions* 20:163-170.
- Dolmierski, R., S. R. Kwiatkowski, and J. Nitka. 1976. Clinical and experimental research into the pathogenesis of toxic effect of styrene. VII. Appraisal of the nervous system in the workers exposed to styrene. *Bull. Inst. Marit. Trop. Med. Gdynia* 27:193-196. [Cumul. Index Med. 18:2040, 1977.]

- Fabry, L., A. Léonard, and M. Roberfroid. 1978. Mutagenicity tests with styrene oxide in mammals. *Mutat. Res.* 51:377-383.
- Fleig, I., and A. M. Thiess. 1978. Mutagenicity study of work employed in the styrene and polystyrene processing and manufacturing industry. *Scand. J. Work Environ. Health* 4(Suppl. 2):254-258.
- Frentzel-Beyme, R., A. M. Thiess, and R. Wieland. 1978. Survey of mortality among employees engaged in manufacture of styrene and polystyrene at the BASF Ludwigschafen works. *Scand. J. Work Environ. Health* 4(Suppl. 2):231-239.
- Gamberale, F., and M. Hultengren. 1974. Exposure to styrene. II. Psychological function. *Work Environ. Health* 11:86-90.
- Götell, P., O. Axelson, and B. Lindelöf. 1972. Field studies human styrene exposure. *Work Environ. Health* 9:76-83.
- Härkönen, H. 1977. Relationship of symptoms to occupational exposure and to the findings of electroencephalographic and psychological examinations. *Int. Arch. Occup. Environ. Health* 40:231-239.
- Harkonen, H. 1978. Styrene, its experimental and clinical toxicology. *Scand J. Work Environ. Health* 4(Suppl. 2):104-113.
- Härkönen, H., K. Lindström, A. M. Seppäläinen, S. Asp, and S. Hänninen. 1978. Exposure-response relationship between styrene exposure and central nervous functions. *Scand. J. Work Environ. Health* 4:53-59.
- Hine, C. H., and V. K. Rowe. 1963. Epoxy compounds. Pp. 1593-1600 in F. A. Patty, ed. *Industrial Hygiene and Toxicology*, 2nd revised edition. Volume 2, Toxicology, D. W. Fassett and J. P. Irish, eds. Interscience, New York.
- James, S. P., and D. A. White. 1967. The metabolism of phenethyl bromide, styrene and styrene oxide in the rabbit and rat. *Biochem. J.* 104:914-921.
- Kankaanpää, J. T. J., K. Hemminki, and H. Vainio. 1979. Embryo-toxicity and teratogenicity of styrene and styrene oxide on chick embryos enhanced by trichloropropylene oxide. *Acta Pharmacol. Toxicol.* 45:399-402.

- Key, M. M., A. F. Henschel, J. Butler, R. N. Ligo, and I. R. Tabershaw, eds. 1977. Occupational Diseases: A Guide to Their Recognition, Revised Edition. DHEW Publication No. (NIOSH) 77-181, p. 242. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio. 608 pp.
- Klimková-Deutschová, E. 1962. Neurologische Befunde in der Plastikindustrie bei Styrol-Arbeitern. (Neurological findings in styrol workers in the plastic industry.) Int. Arch. Gewerbepathol. Gewerbehyg. 19:35-50. [Bulletin of Hygiene 37:811, 1962.]
- Lambotte-Vanderpaer, M., G. Noël, B. Rollmann, M. Mercier, and M. Roberfroid. 1978. Modifying effects of styrene on the catalytic properties of some microsomal enzymes. Arch. Toxicol. Suppl. 1:287-290.
- Larsby, B., R. Tham, L. M. Ödkvist, D. Hydén, I. Bunnfors, and G. Aschan. 1978. Exposure of rabbits to styrene: Electronystagmographic findings correlated to the styrene level in blood and cerebrospinal fluid. Scand. J. Work Environ. Health 4:60-65.
- Leibman, K. C. 1975. Metabolism and toxicity of styrene. Environ. Health Perspect. 11:115-119.
- Lilis, R. W., W. V. Lorimer, S. Diamond, and I. J. Selikoff. 1978. Neurotoxicity of styrene in production and polymerization workers. Environ. Res. 15:133-138.
- Lindström, K., H. Härkönen, and S. Hernberg. 1976. Disturbances in psychological functions of workers occupationally exposed to styrene. Scand. J. Work Environ. Health 2:129-139.
- Lindstrom, K., H. Harkonen, and P. Mantere. 1978. Alcohol consumption and tolerance of workers exposed to styrene in relation to level of exposure and psychological symptoms and signs. Scand. J. Work Environ. Health 4(Suppl. 2):196-199.
- Linnainmaa, K., T. Meretoja, M. Sorsa, and H. Vainio. 1978a. Cytogenetic effects of styrene and styrene oxide. Mutat. Res. 58:277-286.
- Linnainmaa, K., T. Meretoja, M. Sorsa, and H. Vainio. 1978b. Cytogenetic effects of styrene and styrene oxide on human lymphocytes and Allium cepa. Scand. J. Work Environ. Health 4(Suppl. 2):156-162.

- Loprieno, N., A. Abbondandolo, R. Barale, S. Baroncelli, S. Bonatti, G. Bronzetti, A. Cammellini, C. Corsi, G. Corti, D. Frezza, C. Leporini, A. Mazzaccaro, R. Nieri, D. Rosellini, and A. M. Rossi. 1976. Mutagenicity of industrial compounds: Styrene and its possible metabolite styrene oxide. *Mutat. Res.* 40:317-324.
- Loprieno, N., S. Presciuttini, I. Sbrana, G. Stretti, L. Zaccaro, A. Abbondandolo, S. Bonatti, S. Fiorio, and A. Mazzaccaro. 1978. Mutagenicity of industrial compounds. VII. Styrene and styrene oxide: II. Point mutations, chromosome aberrations and DNA repair induction analyses. *Scand. J. Work Environ. Health* 4(Suppl. 2):169-178.
- Lorimer, W. V., R. Lilis, A. Fischbein, S. Daum, H. Anderson, M. S. Wolff, and I. J. Selikoff. 1978. Health status of styrene-polystyrene polymerization workers. *Scand. J. Work Environ. Health* 4(Suppl. 2):220-226.
- Maltoni, C., G. Failla, and G. Kassapidis. 1979. First experimental demonstration of the carcinogenic effects of styrene oxide. *Med. Lavoro* 5:358-362.
- Marniemi, J., E.-M. Suolinna, N. Kaartinen, and H. Vainio. 1977. Covalent binding of styrene oxide to rat liver macromolecules in vivo and in vitro. Pp. 698-702 in V. Ullrich, I. Roots, A. Hildebrandt, R. W. Estabrook, and A. H. Conney, eds. *Microsomes and Drug Oxidations*. Pergamon Press, New York.
- McLaughlin, J., Jr., J. P. Marliac, M. J. Verrett, M. K. Mutchler, and O. G. Fitzhugh. 1963. The injection of chemicals into the yolk sac of fertile eggs prior to incubation as a toxicity test. *Toxicol. Appl. Pharmacol.* 5:760-771.
- McLaughlin, J., Jr., J. P. Marliac, J. Verrett, M. K. Mutchler, and O. G. Fitzhugh. 1964. Toxicity of fourteen volatile chemicals as measured by the chick embryo method. *Am. Ind. Hyg. Assoc. J.* 25:282-284.
- Meretoja, T., H. Vainio, M. Sorsa, and H. Härkönen. 1977. Occupational styrene exposure and chromosomal aberrations. *Mutat. Res.* 56:193-197.
- Meretoja, T., H. Järventaus, M. Sorsa, and H. Vainio. 1978a. Chromosome aberrations in lymphocytes of workers exposed to styrene. *Scand. J. Work Environ. Health* 4(Suppl. 2):259-264.

Meretoja, T., H. Vainio, and H. Järventaus. 1978b. Clastogenic effects of styrene exposure on bone marrow cells of rat. *Toxicol. Lett.* 1:315-318.

Meretoja, T., and H. Vainio. 1979. The use of human lymphocyte tests in the evaluation of potential mutagens: Clastogenic activity of styrene in occupational exposure. Pp. 213-225 in K. Berg, ed. *Genetic Damage in Man Caused by Environmental Agents*. Academic Press, New York.

Milvy, P., and A. J. Garro. 1976. Mutagenic activity of styrene oxide (1,2-epoxyethylbenzene), a presumed styrene metabolite. *Mutat. Res.* 40:15-18.

Nicholson, W. J., I. J. Selikoff, and H. Seidman. 1978. Mortality experience of styrene-polystyrene polymerization workers. *Scand. J. Work Environ. Health* 4(Suppl. 2):247-252.

Norppa, H., E. Elovaara, K. Husgafvel-Pursiainen, M. Sorsa, and H. Vainio. 1979. Effects of styrene oxide on chromosome aberrations, sister chromatid exchange and hepatic drug biotransformation in Chinese hamsters *in vivo*. *Chem. Biol. Interact.* 26:305-315.

Norppa, H., M. Sorsa, and H. Vainio. 1980. Chromosomal aberrations in bone marrow of Chinese hamsters exposed to styrene and ethanol. *Tox. Lett.* 5:241-244.

Ohtsuji, H., and M. Ikeda. 1971. The metabolism of styrene in the rat and the stimulatory effect of phenobarbital. *Toxicol. Appl. Pharmacol.* 18:321-328.

Parkki, M. G. 1978. The role of glutathione in the toxicity of styrene. *Scand. J. Work Environ. Health* 4(Suppl. 2):53-59.

Parkki, M. G., J. Marniemi, and H. Vainio. 1976. Action of styrene and its metabolites styrene oxide and styrene glycol on activities of xenobiotic biotransformation enzymes in rat liver in vivo. *Toxicol. Appl. Pharmacol.* 38:59-70.

Parkki, M. G., J. Marniemi, T. Ekfors, A. Louhivuori, and A. Aitio. 1978. Hepatotoxic changes in hamster by styrene. Pp. 320-322 in J. R. Fouts and I. Gut, eds. *Industrial and Environmental Xenobiotics: In Vitro Versus In Vivo Biotransformation and Toxicity*. Proceedings of an International Conference held in Prague, Czechoslovakia, September 13-15, 1977. *Excerpta Medica*, Amsterdam, The Netherlands.

- Proctor, N. H., and J. P. Hughes. 1978. Styrene. Pp. 449-450 in Chemical Hazards of the Workplace. J. B. Lippincott, Philadelphia, Penna.
- Ragule, N. 1974. Embryotropic action of styrene. Gig. Sanit. No. 11:85-86. [Chem. Abs. 82:81357q, 1975.]
- Roberfroid, M., F. Poncelet, M. Lambotte-Vandepaer, M. Duverger-Van Bogaert, C. de Meester, and M. Mercier. 1978. Acute biotoxic effect of styrene on rat liver: Correlation with enzyme-mediated mutagenicity of benzpyrene and acrylonitrile. Scand. J. Work Environ. Health 4(Suppl. 2):163-168.
- Rosén, I., B. Haeger-Aronsen, S. Rehnström, and H. Welinder. 1978. Neurophysiological observations after chronic styrene exposure. Scand. J. Work Environ. Health 4(Suppl. 2):184-194.
- Roth, B., and E. Klimková-Deutschová. 1963. The effect of the chronic action of industrial poisons on the electroencephalogram of man. Rev. Czech. Med. 9:217-227. [Cumulated Index Medicus 5:N-1123, 1964.]
- Savolainen, H., M. Helojoki, and M. Tengén-Junnila. 1980. Behavioural and glial cell effects of inhalation exposure to styrene vapour with special reference to interactions of simultaneous peroral ethanol intake. Acta Pharmacol. Toxicol. 46:51-56.
- Savolainen, H., and P. Pfaffli. 1977. Effects of chronic styrene inhalation on rat brain protein metabolism. Acta Neuropathol. (Berl.) 40:237-241. [Cumulated Index Medicus 19:3935, 1978.]
- Savolainen, M., and P. Pfaffli. 1978. Accumulation of styrene monomer and neurochemical effects of long-term inhalation exposure in rats. Scand. J. Work Environ. Health 4(Suppl. 2):78-83.
- Seppäläinen, A. M. 1978. Neurotoxicity of styrene in occupational and experimental exposure. Scand. J. Work Environ. Health 4(Suppl. 2):181-183.
- Seppäläinen, A. M., and H. Härkönen. 1976. Neurophysiological findings among workers occupationally exposed to styrene. Scand. J. Work Environ. Health 2:140-146.
- Shugaev, B. B. 1969. Concentrations of hydrocarbons in tissues as a measure of toxicity. Arch. Environ. Health 18:878-882.
- Smyth, H. F., Jr., C. P. Carpenter, C. S. Weil, and U. C. Pozzani. 1954. Range-finding toxicity data. List V. AMA Arch. Ind. Hyg. Occup. Med. 10:61-68.

- Society of the Plastics Industry, Inc. 1979. Investigation of Workers Exposed to Styrene in the Reinforced Plastics Industry. Report of a study conducted by the University of Cincinnati under contract to The Society of the Plastics Industry, Inc., New York.
- Spencer, H. C., D. D. Irish, E. M. Adams, and V. K. Rowe. 1942. The response of laboratory animals to monomeric styrene. J. Ind. Hyg. Toxicol. 24(10):295-301.
- Spirtas, R., M. Van Ert, J. F. Gamble, P. Wolf, and A. J. McMichael. 1976. Toxicologic, industrial hygiene and epidemiological considerations in the possible association between SBR manufacturing and neoplasms of lymphatic and hematopoietic tissues. Pp. 67-112 in L. Ede, ed. Proceedings of NIOSH Styrene-Butadiene Briefing, Covington, Ky., April 30, 1976. HEW Publication No. (NIOSH) 77-129. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio.
- Stewart, R. D., H. C. Dodd, E. D. Baretta, and A. W. Schaffer. 1968. Human exposure to styrene vapor. Arch. Environ. Health 16:656-662.
- Stoltz, D. R., and R. J. Withey. 1977. Mutagenicity testing of styrene and styrene epoxide in Salmonella typhimurium. Bull. Environ. Contam. Toxicol. 17:739-742.
- Sugimura, K., T. Kimura, and M. Goto. 1978. Mutagenicities of styrene oxide derivatives on Salmonella typhimurium (TA 100). Relationship between mutagenic potencies and chemical reactivity. Mutat. Res. 58:159-165.
- Taulbee, J., D. Andjelkovic, T. Williams, J. F. Gamble, and P. Wolf. 1976. A study of possible association between exposure to SBR processes and mortality from leukemia and related diseases based on toxicologic, industrial hygiene and epidemiologic considerations (for workers in the 1951 and 1964 cohorts and deaths 1964-1973). Pp. 113-162 in L. Ede, ed. Proceedings of NIOSH Styrene-Butadiene Briefing, Covington, Ky., April 30, 1976. HEW Publication No. (NIOSH) 77-129. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio.
- U.S. Department of Health, Education, and Welfare. 1979. Bioassay of Styrene for Possible Carcinogenicity. NIH Publication No. 79-1741. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, Md. 46 pp. + A-1 to D-11.

- Vainio, H. 1978. Vinyl chloride and vinyl benzene (styrene)--metabolism, mutagenicity and carcinogenicity. Chem. Biol. Interact. 22:117-124.
- Vainio, H., and E. Elovaara. 1979. The interaction of styrene oxide with hepatic cytochrome P 450 in vitro and effects of styrene oxide inhalation on xenobiotic biotransformation in mouse liver and kidney. Biochem. Pharmacol. 28:2001-2004.
- Vainio, H., and A. Makinen. 1977. Styrene and acrylonitrile induce depression of hepatic nonprotein sulfhydryl content in various rodent species. Res. Commun. Chem. Pathol. Pharmacol. 17:115-124.
- Vainio, H., R. Pääkkönen, K. Rönholm, V. Raunio, and O. Pelkonen. 1976. A study on the mutagenic activity of styrene and styrene oxide. Scand. J. Work Environ. Health 3:147-151.
- Vainio, H., K. Hemminki, and E. Elovaara. 1977. Toxicity of styrene and styrene oxide on chick embryos. Toxicology 8:319-325.
- Watabe, T., M. Isobe, T. Sawahata, K. Yoshikawa, S. Yamada, and E. Takabatake. 1978. Metabolism and mutagenicity of styrene. Scand. J. Work Environ. Health 4(Suppl. 2):142-155.
- Weil, C. S., N. Condra, C. Haun, and J. A. Striegel. 1963. Experimental carcinogenicity and acute toxicity of representative epoxides. Am. Ind. Hyg. Assoc. J. 24:305-325.
- Wilson, R. H. 1944. Health hazards encountered in the manufacture of synthetic rubber. J. Am. Med. Assoc. 124:701-703.
- Wolf, M. A., V. K. Rowe, D. D. McCollister, R. L. Hollingsworth, and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Experiments on laboratory animals. AMA Arch. Ind. Health 14:387-398.

BIOLOGICAL EFFECTS IN NONMAMMALIAN SPECIES

Data concerning the biological effects of alkyl benzenes in nonmammalian species, particularly the effects likely to result from exposure to environmental concentrations, are few and far between. Most investigators have used relatively high concentrations of the test compounds in studies to establish acute toxicity values or thresholds with aquatic vertebrates and invertebrates, microbial species, plants, and, to a more limited extent, insects. Information on avian species appears to be nonexistent. There is virtually no information on chronic effects that might result from continuous low-level or intermittent exposure to chemicals of this type or on possible long-term effects on populations of various species.

EFFECTS OF ALKYL BENZENES ON AQUATIC ORGANISMS

There is a general consensus that, in addition to several carcinogenic polycyclic aromatics, the volatile, water-soluble, aromatic hydrocarbons present a potential environmental hazard to a wide variety of aquatic organisms. Although the monocyclic aromatics such as toluene, xylenes, cumene, and ethylbenzene are major toxic water-soluble components of petroleum (Tables 4-9 and 4-10), only limited attention has been given to quantitation of these compounds in marine and freshwater environments (McAuliffe, 1976, 1977b; Sauer et al., 1978). Toxicity studies have often been conducted on uncharacterized water-soluble fractions of various crude oils, but investigators have paid little attention to measurements of concentrations before, during, or after the experiments to account for rates of evaporation of individual components. From the few controlled studies that have been conducted with single hydrocarbons, it is often difficult to assess how the toxicities relate to those likely to occur in natural aquatic environments.

Effects on Vertebrates (Fish)

The acute toxicities to fish exposed to one or more of several alkyl benzenes have been reported by Pickering and Henderson (1966). The 96-hr LC₅₀ values observed by these investigators fall within the range of 20-97 mg/liter (Table 8-1), but the 95% confidence limits are considerable and the values can only be considered approximations. Nonetheless, they are in general agreement with an earlier report that the orange spotted sunfish (Lepomis humilis) died within 1 hr after exposure to a toluene concentration of 61-65 mg/liter (Shelford, 1917). The tests conducted by Pickering and Henderson (1966

TABLE 8-1. Acute (96-hr) Toxicity of Alkyl Benzenes to Different Species of Freshwater Fish^a

Species	96-hr Median Tolerance Limits (LC ₅₀ and 95% Confidence Limits (mg/liter)			
	Toluene	Xylene	Ethylbenzene	Styrene
Fathead minnow (<u>Pimephales promelas</u>)	34.27 (22.83-45.86)	26.7 (23.53-29.97)	48.51 (38.90-62.83)	46.41 (37.11-59.54)
Bluegill sunfish (<u>Lepomis macrochirus</u>)	24.00 (18.88-30.51)	20.87 (15.99-26.18)	32 (32.00-32.00)	25.05 (19.03-33.53)
Goldfish (<u>Carassius auratus</u>)	57.68 (48.87-68.75)	36.81 (32.64-42.69)	94.44 (79.62-110.1)	64.74 (57.17-75.48)
Guppy (<u>Lebistes reticulatus</u>)	59.30 (50.87-70.34)	34.73 (30.26-40.75)	97.10 (81.45-114.6)	74.83 (58.75-95.32)

^aData from Pickering and Henderson, 1966.

were conducted under static conditions in soft water (20 mg/liter as calcium carbonate) at pH 7.5 although the results of similar tests conducted in hard water (360 mg/liter as calcium carbonate) showed that hardness had little effect on toxicity. Since the 96-hr LC₅₀ values were similar to those measured at 24 hr, it would appear that most of the toxicity occurred during the first 24 hr. Indeed, most of the alkyl benzenes were probably lost rapidly through evaporation (see pp. 206-207). No attempts were made to measure the actual concentrations during the test period. As a result, the LC₅₀ values reported by Pickering and Henderson (1966) may be rather high. This conclusion is supported by studies with goldfish (Carassius auratus), in which considerably lower 96-hr LC₅₀ values of 22.8 mg/liter and 16.94 mg/liter were measured for toluene and xylene, respectively, in a flow-through bioassay with measured concentrations of the test compounds (Brenniman et al., 1976). On the other hand, the results of the studies of Pickering and Henderson (1966) may better approximate the toxicity under natural conditions where evaporation and dissolution will occur and where concentrations of volatile aromatics can be expected to change considerably with time (National Academy of Sciences, 1975a).

Rainbow trout (Salmo gairdneri) exposed to continuous flows of xylene in water survived a concentration of 7.1 mg/liter, but suffered 100% mortality at 16.1 mg/liter (Walsh et al., 1977). For this compound the calculated 24- and 96-hr LC₅₀'s to rainbow trout were both 13.5 mg/liter. Confidence intervals ranged from 9.5 to 19.2 mg/liter. Fish were stressed at concentrations as low as 3.6 mg/liter. After a 1.5-hr exposure to 7.1 mg/liter xylene, more than 90% lost equilibrium, an effect as potentially important as mortality with respect to environmental impact.

Folmar (1976) reported that the fry of rainbow trout actively avoid xylene concentrations as low as 0.1 mg/liter. Such chemically induced avoidance could have serious implications for the availability of food and habitat and for migration patterns.

Volatile hydrocarbons may persist in certain aquatic environments by binding to suspended particulates in the water. Although this tends to slow evaporation rates, it may protect aquatic organisms when the suspended solids are not an item of food. This may explain the high 96-hr LC₅₀ value for toluene of 1,180 mg/liter, which has been reported for mosquitofish (Gambusia affinis) in turbid water (Wallen et al., 1957).

Few studies have been conducted with saltwater fish. Striped bass (Morone saxatilis) succumbed rapidly to lethal concentrations of toluene, ethylbenzene, and o-, m- and p-xylene at 96-hr LC₅₀ values of 7.3, 4.3, 11, 9.2, and 2 mg/liter, respectively (Benville

and Korn, 1977). At concentrations between 20 and 100 mg/liter, benzene, toluene, xylene, and ethylbenzene quickly caused rapid, violent, and erratic swimming of young coho salmon (Oncorhynchus kisutch) within 15 to 20 minutes. This was followed by "coughing," loss of equilibrium, and death. Most of the deaths occurred during the first few hours after exposure. Fish surviving this period usually survived the experiment (Morrow et al., 1975). The investigators suggested that toxicity might result from solubilization of fats from the gill membranes of fish with consequent increases in permeability and uptake of ions from the hypertonic environment. This was supported by rapid increases of monovalent ions in the blood of fish exposed to the alkyl benzenes.

Studies have shown that sheepshead minnow (Cyprinodon variegatus) exposed to toluene had a 96-hr LC_{50} of 277-485 mg/liter (U.S. Environmental Protection Agency, 1978), which demonstrates considerably more resistance than shown by other species on which data are available. An embryo-larval test indicated a chronic LC_{50} of 2.1 mg/liter when the observed adverse effect pertained to hatching and survival (U.S. Environmental Protection Agency, 1978, 1979).

Stoss and Haines (1979) exposed fertilized eggs and newly hatched fry of the Japanese medaka (Oryzias latipes) to the water-soluble extracts of toluene by static bioassay. They established a mean 96-hr LD_{50} of 54 mg/liter for developing embryos. Embryos in early (<3.5 hr) and later (>192 hr) stages of development were more sensitive than the average, and newly hatched fry were more tolerant to toluene. Exposure of 2- to 17-hr-old embryos to concentrations of toluene as low as 41 mg/liter induced severe embryonic deformities such as abnormalities in the heart and circulatory system and deformation of the eyes. Higher concentrations caused abnormalities of the tail musculature and visceral organs. The period during which these deformities occurred was correlated with gastrulation and the onset of organogenesis.

Toluene was absorbed rapidly from water into the Pacific herring (Clupea harengus pallasi). Maximum tissue levels were attained within 24 hr. In their gallbladders, which contained the highest residues (34 mg/kg), toluene reached a concentration 340 times greater than that measured in the water (0.1 mg/liter) (Korn et al., 1977). There were no detectable amounts in most tissues 1 to 2 days after termination of exposure, indicating that residues were depurated rapidly. This was not true for the gallbladder, intestine, and pyloric caeca, which retained detectable levels through the seventh day after the exposure was terminated. The investigators suggested that slow depuration from the gallbladder may reflect metabolism in the liver and storage of metabolites in the gallbladder.

Eels (Anguilla japonica) reared in seawater containing a crude oil suspension (50 mg/liter) accumulated aromatics in their flesh. Concentration ratios (eel flesh:water) of toluene, m- or p-xylene, and o-xylene at 10 days were 13.2, 23.6, and 21.4, respectively (Ogata and Miyake, 1979). Half-lives for these compounds were 1.4, 2.6, and 2.0 days, respectively, after transfer to clean seawater. The concentrations in which alkyl benzenes accumulated were somewhat higher than those reported by Ogata and Miyake (1973), who studied mixtures of toluene and xylenes. The higher concentrations may be attributable to the apparently low rate at which these compounds are metabolized to the corresponding benzyl alcohol derivatives (Ohmori et al., 1975).

Toluene has been identified as one compound imparting the offensive odor to fish exposed to aromatic hydrocarbons (Ogata and Miyake, 1973). Fish whose muscle contained toluene at 0.25 mg/kg possessed an offensive odor (Funasaka et al., 1975). The U.S. Environmental Protection Agency (1978) determined that this concentration was the taste threshold in deep-fried flesh of yellow perch (Perca flavescens) that had been exposed to toluene for 7 days.

There was a very discernible taste in the flesh of rainbow trout exposed continuously to concentrations of xylene as low as 0.36 mg/liter for 56 days (Walsh et al., 1977). The degree of off-taste was correlated directly with the residues of xylene that were detected by gas chromatography. The flavor returned to normal within 2 to 3 days after the fish were placed in untreated water.

The incidence of a variety of tumors found in fish from the Fox River watershed in Wisconsin and Illinois was 4.38%, compared with 1.03% for fish examined from an unpolluted Canadian watershed (Brown et al., 1973). Toluene was among a partial list of 12 organic pollutants found in the Fox River.

Effects on Invertebrates. Acute (24-hr) studies with brine shrimp (Artemia salina) have established LC₅₀'s of 66, 68, 33, and 110 mg/liter for benzene, styrene, toluene, and cumene, respectively (Price et al., 1974). These concentrations are considerably higher than the 24-hr LC₅₀'s of 2.0, 2.2, 4.8, 5.3, and 12 µl/liter (approximately equal to mg/liter) for p-xylene, ethylbenzene, m-xylene, o-xylene, and toluene, which were reported for bay shrimp (Crago franciscorum) (Benville and Korn, 1977), but they are in general agreement with the 24-hr LC₅₀ of toluene to adult and larval stages of the grass shrimp (Palaemonetes pugio) (17.2-38.1 mg/liter) (Potera, 1975; U.S. Environmental Protection Agency, 1978, 1979) and the mysid shrimp (Mysidopsis bahia) (56.3 mg/liter) (U.S. Environmental Protection Agency, 1978, 1979). In similar tests with a copepod (Nitocra spinipes), a 24-hr LC₅₀ for toluene was found to be between 24.2 and 74.2 mg/liter (Potera, 1975; U.S. Environmental Protection Agency, 1979).

The water flea (Daphnia magna) appears to be the only freshwater aquatic invertebrate tested. The 48-hr LC_{50} of 313 mg/liter for toluene established for this species indicates that it is considerably more tolerant than the saltwater species (U.S. Environmental Protection Agency, 1978, 1979).

Acute (1-hr) experiments showed that the water fractions of several crude oils and aromatic hydrocarbons were toxic to free-swimming larvae (nauplii) of the barnacle (Balanus amphitrite niveus) (Donahue et al., 1977). The substituted benzenes and naphthalenes were among the most toxic of the single aromatics tested. In seawater that was 60% saturated with either xylene or cumene, most of the larvae were killed. A depression of phototactic response was observed at lower concentrations.

Toluene exhibited no toxicity to the mussel (Mytilus edulis) at concentrations up to 1 mg/liter (Lee et al., 1972). It was taken up by the gill tissues, however, and was subsequently transferred to the mantle, adductor muscle, and the gut. There was no evidence of metabolism. Transfer of treated mussels to fresh seawater resulted in the discharge of most of the material from the tissues.

Exposure of fertilized eggs or young embryos of two species of sea urchin (Paracentrotus lividus and Psammechinus microtuberculatus) to high concentrations of styrene ($5 \times 10^{-4}M$, 52 mg/liter) resulted in abnormal differentiation of the embryos (Pagano et al., 1978). Other experiments showed that exposure of eggs or sperm to styrene ($10^{-4}M$, 104 mg/liter) for 2 and 5 minutes, respectively, prior to insemination also resulted in abnormal embryonic development. At a concentration of $10^{-3}M$ (1,040 mg/liter), styrene interfered with the fertilizing capacity of the sperm. These effects were induced during the few minutes of contact, since both eggs and sperm were thoroughly washed in fresh seawater prior to insemination. The investigators concluded that styrene interferes directly with the genome. However, nonspecific effects cannot be ruled out at these relatively high concentrations.

EFFECTS OF ALKYL BENZENES ON MICROBIAL ORGANISMS

Long recognized for its antimicrobial properties, toluene has been used by microbiologists for many years to sterilize cultures. Within 24 hr, a 0.4% (4,000 mg/liter) solution of toluene completely sterilized a urine sample containing Escherichia coli and Pseudomonas fluorescens (Sabalitschka and Preuss, 1954). A toxicity threshold of 200 mg/liter toluene has been reported for E. coli by Bringham and Kühn (1959).

At concentrations of 500 to 1,000 mg/liter, xylene eliminated rot (Phymatotrichum omnivorum) on plants and caused the plants' as well (Ezekial and Taubenhaus, 1935). As measured by rates of methane evolution, low levels of toluene (20 mg/liter) appear to increase the growth rate of bacteria in sewage sludge deposits, but at higher concentrations (200 mg/liter) a toxic effect was observed (Barash, 1957). Similarly, low levels of toluene and xylene in the vapor phase allowed rapid growth of Pseudomonas putida (AB) and Micrococcidia sp., but they were toxic at saturation levels (Gibson, 1961). At a sublethal concentration (0.1%, 1,000 mg/liter) toluene elicited a negative chemotactic response in each of four motile marine bacteria (Pseudomonads) (Young and Mitchell, 1973). At 0.6% (6,000 mg/liter) all chemotactic responses were inhibited (Mitchell et al., 1973).

Toluene has also been used extensively as an unmasking agent in microbiological research. It allows the in-vitro assay of several intracellular enzymes using exogenous substrates (De Smet et al., 1978; Jackson and DeMoss, 1965). This use depends on the ability of toluene to render bacteria permeable to a variety of low molecular weight compounds and several macromolecules while remaining impermeable to proteins larger than approximately 50,000 daltons (De Smet et al., 1978). In studies with E. coli, De Smet et al. (1978) established that a 0.25% (2,500 mg/liter) solution of toluene partially dissolved the inner cytoplasmic membrane and displaced intracellular material to the periphery of the cell (Woldringh, 1973).

Both toluene and xylene changed the asymmetric unit membrane profile to a symmetric profile in vegetative cells of Bacillus subtilis and caused the appearance of gaps in the membrane (Silva et al., 1978). The cells did not appear to be lysed by toluene, although the cytoplasm collapsed to the interior. Moreover, 85% of the ribonucleic acid (RNA), most of which resulted from the aggregation of ribosomes, and up to 25% of the total protein, including a variety of different enzymes (De Smet et al., 1978; Jackson, 1974; Jackson and DeMoss, 1965), were lost to the surroundings.

De Smet et al. (1978) suggested that although the toluene attacks primarily the inner cytoplasmic membrane, the actual loss of intracellular material depends on the integrity of the outer membrane. E. coli cells treated with 10% (100,000 mg/liter) toluene in the presence of magnesium, which stabilizes the outer membrane, lost very little intracellular material. In comparison, control cells lost large amounts of protein, phospholipid, and lipopolysaccharide when treated in the presence of ethylenediaminetetraacetic acid (EDTA), which increases the permeability of the outer membrane. At a concentration of 10% (100,000 mg/liter) toluene, the magnesium appeared to have a protective effect and there was total disorganization of the cytoplasmic membrane.

PHYTOTOXICITY OF ALKYL BENZENES

The phytotoxic action of a variety of light petroleum oils and aromatic solvent mixtures has long been recognized and has been exploited to control submerged aquatic weeds (Bruns et al., 1955; Frank et al., 1961). Although there have been studies with uncharacterized oil mixtures, phytotoxicity is generally attributed to the presence of aromatic hydrocarbons with low boiling points, particularly benzene, toluene, xylenes, and other alkyl benzenes.

Working with individual compounds in the vapor phase and following spray treatments, Currier (1951) showed that phytotoxicity increased in the following order. benzene > toluene > xylene > trimethylbenzene. When the concentration of toluene vapors was increased from $0.69 \times 10^{-4}M$ to $4.9 \times 10^{-4}M$ (6.3-45 ppm) in air, there was a progressive increase in toxicity to young barley plants. A half-hour exposure at the lowest concentration caused damage to approximately 50% of the plants (measured after 24 hr), whereas the highest concentration killed almost all of the plants after only a 7- to 15-minute exposure. Some recovery was observed from 1 to 4 weeks after exposure to the lowest concentration or after very short exposures to the highest concentration.

Currier (1951) also observed that xylenes in a concentration of $0.46 \times 10^{-4}M$ (4.9 ppm) in air caused the same degree of injury to barley plants as toluene caused at $1.3 \times 10^{-4}M$ (11.9 ppm). Even the lowest vapor phase concentrations were approximately two orders of magnitude greater than those measured in polluted urban air (Table 4-1). Therefore, acute phytotoxic effects are unlikely to occur under most environmental conditions. The phytotoxicity of xylene appears to depend on the type of application. When applied as a spray to alfalfa, tomatoes, dwarf corn, squash, potatoes, and beans, xylene produced no visible injury at concentrations up to 1,480 mg/liter, and there was no effect on crop yield or growth rate (Miller et al., 1976).

Different species of plants vary considerably in their susceptibility to toluene, xylene, and, presumably, other alkyl benzenes. Thus, carrots and other members of the Umbelliferae family, including parsnip, celery, dill, and parsley, are considerably less susceptible than barley to injury from toluene and xylene vapors, whereas tomato plants appear to be particularly sensitive (Currier, 1951). A similar conclusion was reached by Dallyn and Sweet (1951) who showed that carrots were considerably more tolerant than beans to the phytotoxic effects of Stoddard solvent (mainly aromatics) and that grasses were quite susceptible. They suggested that these differences in susceptibility might provide a satisfactory basis for the selective weeding of certain crops. The sensitivity of certain species of trees to xylene is indicated by the severe injury

observed in maple, elm, and chinaberry after their roots were treated with xylene in concentrations of 500-1,000 mg/liter to control root rot (Phymatotrichum omnivorum) (Ezekial and Taubenhaus, 1935; Miller et al., 1976).

Photosynthetic organisms such as algae and marine phytoplankton are important to freshwater and marine ecosystems. Consequently, several studies have been conducted to determine their response to soluble aromatics that might originate from oil spills. Growth of the freshwater unicellular green algae (Chlorella vulgaris) was inhibited by both toluene and *o*-xylene. The number of algal cells was reduced by 50% after exposure to toluene at 245 mg/liter and *o*-xylene at 55 mg/liter (Kauss and Hutchinson, 1975). The short-term growth inhibition observed with aqueous extracts of several different crude oils was probably caused by aromatic components with low boiling points of the oils that were rapidly lost through evaporation.

The addition of styrene (100-500 mg/liter) to aqueous media containing cultures of 13 species of algae resulted in no overt effects on vitality or growth (Munjko and Grbić, 1977). Inhibition of growth of two of the 13 species was observed at 1,000 mg/liter, and all were affected deleteriously at 5,000 mg/liter.

Styrene also affects the growth of various moulds (Munjko and Grbić, 1977) although at concentrations considerably higher than those likely to be encountered in the environment. The growth of 14 species of moulds on Sabouraud's agar was affected only slightly in the presence of styrene at 5,000 to 10,000 mg/liter, but severe effects on both growth and pigmentation were observed at concentrations of 50,000 and 100,000 mg/liter. In subsequent studies with pure cultures of several strains of Streptomyces isolated from a variety of soil and water sources, Grbić and Munjko (1977) confirmed that exposure to styrene caused deleterious effects on growth, morphological characteristics, and pigmentation. Strains isolated from soils were most sensitive to the effects of styrene. None would grow in the presence of 50,000 mg/liter styrene, and their growth was inhibited at 20,000 mg/liter. Strains isolated from water were apparently more resistant to styrene and were able to grow in the presence of concentrations of up to 20,000 or 30,000 mg/liter. These strains appeared to be capable of utilizing styrene as a sole carbon and energy source (Grbić and Munjko, 1977).

Dunstan et al. (1975) conducted experiments with four phylogenetically different phytoplankton--a diatom (Skeletonema costatum), a dinoflagellate (Amphidinium carteri), a coccolithophorid (Cricosphaera carterae), and a green flagellate (Dunaliella tertiolecta). These organisms showed varied growth responses when exposed to a range of concentrations of toluene and xylene in enclosed seawater cultures at 18°C. Growth of all four species was significantly

inhibited by xylene and toluene in concentrations exceeding 100 mg/liter. At lower concentrations, growth was considerably stimulated in some species. The effect varied with both the species and the test compound. The investigators suggested that such variable effects on algae could have significant ecological effects through altering the structure of the natural populations, but field validation is lacking. Currier (1951) reported that low concentrations of toluene and xylene also stimulate the growth of higher plants. Tomato cuttings placed in Hoagland's solution 1% or 10% saturated with either toluene or xylene developed roots more extensively and earlier than did controls, whereas solutions saturated with either material inhibited root formation and the stem died. Morré et al. (1965) reported that xylene had similar effects on seedlings of maize (Zea mays). At concentrations of 100 to 500 mg/liter, xylene prolonged the life of many types of cut flowers (Bhatt, 1964).

Alkyl benzenes have a variety of other effects on plants, especially with respect to seed germination. Germination of the seeds of bean, squash, radish, oat, and lettuce was retarded for 6 to 30 days following application of xylene at levels of 500 to 2,000 qt/acre (4,750 liters/hectare) (Beetle, 1951). This effect may be related to the changes in water uptake observed in toluene-treated seeds of plants such as corn and peas (Pringsheim, 1930). However, sprouting of dormant potato tubers was accelerated after soaking them in xylene or exposing them to xylene vapor for 16 to 24 hr (Denny, 1926). Sweet potatoes treated similarly with toluene vapor formed a hardened outer covering (Miwa et al., 1946). Most of these effects probably reflect the ability of alkyl benzenes to change the permeability of the cell membrane or the outer seed coat.

Most of the observed plant injuries in response to toluene and xylene are acute rather than chronic. The chemicals appear to enter the plant readily, probably through the stomata or cuticle, and act strictly as contact poisons, i.e., they quickly kill the tissues with which they came into contact. They do not seem to accumulate and, in most cases, are not translocated in the plant.

When a solvent comes into contact with a tissue, it affects the external plasma membrane by causing a breakdown of the physical organization of the protoplasm, an increase in permeability, and a leakage of cell sap into intercellular spaces. The overall effect is a contraction and shrinking of the cell wall and, finally, a general collapse of the leaf structure similar to that observed following severe desiccation. The signs of toxicity vary among different plant tissues although all effects are attributed to the destruction of the plasma membrane and the consequent disruption of its semipermeable properties. In green leaves this results in a darkening of the leaf tips, loss of turgor, and a destruction

(bleaching) of chlorophyll in sunlight (Currier, 1951; Kauss and Hutchinson, 1975). The bleaching effect is undoubtedly responsible for the reduced photosynthesis observed in some species, e.g., in the giant kelp (Macrocystis pyrifera) following exposure to 10 mg/liter toluene (North et al., 1959). Toluene also disrupts the internal morphology of the green alga Chlamydomonas reinhardtii (Howell and Walker, 1972) and attacks the cytoplasmic membrane of the fungus Saccharomyces cerevisiae (Vas, 1953).

Lerner et al. (1978) established that toluene induces the formation of "pores" in plant cell membranes. They showed that such pores in the cell membranes of roots of a shrub (Atriplex nummularia) were 0.5 to 0.7 nm in radius since sugars, amino acids, and short chain organic acids could diffuse relatively freely through them, whereas NaD could not.

The phytotoxic effects of toluene, xylene, and probably other alkyl benzenes are thought to result from a biophysical rather than a biochemical action. As a result of their studies with a green alga (Chlorella vulgaris), Kauss and Hutchinson (1975) suggested that the alkyl benzenes act as structurally nonspecific physical toxicants that exert equitoxic effects when there is thermodynamic equilibrium between the intracellular and extracellular phases (Ferguson, 1939). Thus, the toxicity to Chlorella vulgaris of benzene, toluene, and xylene increases with decreasing aqueous solubility, and equitoxic effects are observed when the compounds are present at the same relative saturation (an approximate measure of thermodynamic activity). If this is true, alkyl benzenes such as ethylbenzene, cumene, and styrene can be expected to have equal or somewhat greater phytotoxicities than do toluene and xylene.

EFFECTS OF ALKYL BENZENES ON INSECTS

Most aromatic hydrocarbons with low boiling points are toxic to a variety of insect species that are exposed to a vapor or via direct contact. Moore (1917) reported that toluene and xylene, when added to 1-liter flasks in concentrations of 10 to 15 mg or 5 to 10 µg, respectively, were lethal to houseflies (Musca domestica). These materials are also toxic to the blowfly (Lucilia sericata), the German cockroach (Blattella germanica), and the Colorado potato beetle (Leptinotarsa decemlineata). Xylene is toxic to the American cockroach (Periplaneta americana) following injection (Munson and Yeager, 1945). Topical (contact) application of only 0.2 µl xylene to the ventral abdomen of 3-day-old houseflies caused immediate knockdown of the insect and violent tremors. One hundred percent mortality was recorded 24 hr after treatment (Kocher and Ascher, 1954). When 0.4 µl of toluene was applied, the investigators re-

ported similar knockdown and tremors and a 25% mortality 24 hr afterward. Since much of the dose applied in this way is presumably lost through vaporization, the toxicity of these materials is surprisingly high. Further tests should be conducted to confirm these data.

The LD₅₀'s of benzene, toluene, and xylene to fourth instar mosquito larvae (Aedes aegypti) were established at 59, 22, and 14 mg/liter, respectively. Nonlethal threshold doses for these materials were 13, 10, and 8 mg/liter (Berry and Brammer, 1977). In another study, a significant increase in oxygen consumption was observed in mosquito larvae following exposure to sublethal doses of the water-soluble fractions from whole gasoline (Berry et al., 1978). Since the effect was observed only in feeding larvae, the investigators suggested that the water-soluble gasoline fractions were absorbed onto the food particles and ingested. Tests conducted separately with benzene, toluene, and xylene showed no increase in respiration in either feeding or nonfeeding larvae. An increased oxygen consumption observed in the presence of a combination of benzene and toluene suggested that there might be synergism between these two compounds, which could explain the effect observed with whole gasoline. In another part of this study, ³H-toluene was absorbed rapidly (within 1 to 4 hr) from the water by the mosquito larvae and was subsequently eliminated equally as rapidly. However, traces of the material remained in the tissues for at least 12 hr, even after the larvae were transferred to clean distilled water.

Several aromatic hydrocarbons were used by Ferguson and Pirie (1948), who conducted a comprehensive study of grain weevils (Calandra granaria) to determine the vapor phase toxicity of approximately 100 different materials (Table 8-2). Their results indicate that the toxicities of the alkyl-substituted aromatic hydrocarbons increase with increasing boiling point (decreasing vapor pressure) and with the size of the alkyl substituent on the aromatic ring. These results were confirmed by the studies of Moore (1917) and Berry and Brammer (1977). As a result of these and other data indicating the relative constancy of the Pt:Ps ratio (which approximates thermodynamic activity) at the LD₅₀'s, Ferguson and Pirie (1948) suggested that the aromatic hydrocarbons are among the compounds that can be classified as structurally nonspecific physical poisons. The toxicity of such compounds is ascribed to a physical narcotic mechanism that results from the establishment of an equilibrium between the intracellular phase and that external to the insect. They produce 50% mortality at thermodynamic activities ranging from 0.1 to 1.0, irrespective of their chemical structures. Since toxicity depends on a distribution equilibrium, it is usually reversible, although prolonged exposure may lead to irreversible damage.

TABLE 8-2. Toxicity of Aromatic Hydrocarbons to Grain Weevils^a

Compound	Saturated Vapor Pressure, mm at 25°C (Ps)	LD ₅₀ mg/liter	10 ⁻⁶ g mol/liter	Pt/Ps ^b
Benzene	93.9	210	2690	0.53
Toluene	28.5	96	1040	0.68
Ethylbenzene	9.6	50	470	0.90
Propylbenzene	3.5	30	250	~1.0
Butylbenzene	1.2	<50% kill at saturation		
<u>o</u> -Xylene	6.64	31	290	0.82
<u>p</u> -Xylene	8.87	48	450	0.95
Mesitylene	2.9	~25	~200	~1.0
Pseudocumene	1.7	<50% kill at saturation		

^aFrom Ferguson and Pirie, 1948.^bPt is the vapor pressure of the test compound (mm at 25°C) at the LD₅₀. Pt/Ps approximates the thermodynamic activity.

Slifer (1946) reported that xylene and toluene prevent or terminate diapause in eggs of the grasshopper (Heteranoplos differ-
entialis). This effect, which is observed after eggs are placed directly in the solvents for approximately 30 minutes, is undoubtedly due to the removal of the cuticular waxes that protect the egg and maintain appropriate permeability characteristics. Following treatment with xylene, the eggs gain or lose water much more rapidly than normal. The effect of the solvent is more apparent on the outer, cuticular layer in the region of the hydropyle, the structural part of the egg through which water is taken up.

CONCLUSIONS

An evaluation of the data from the relatively few studies that have been conducted indicates that high concentrations of alkyl benzenes produce toxic effects in a variety of living organisms. Although chronic studies have not been conducted, most of the toxicity appears to be acute and results from a rather nonspecific action causing a breakdown in the structure and functional integrity of biological membranes. The evidence suggests that the alkyl benzenes can be classified within the large group of nonspecific narcotic agents and that their action is related more to their physical or colligative properties than to the presence of specific structural characteristics. Consequently, the biological activity of the alkyl benzenes can be expected to increase with the number and/or size of the alkyl substituents, and their acute effects are likely to be reversible unless exposure involves extremely high concentrations, which result in a total disruption of membrane function and a consequent breakdown in cell organization. This type of toxic action will probably be observed with all types of living organisms.

Except under unusually severe circumstances, e.g., near major spills or other sources of pollution, concentrations of alkyl benzene in the environment are considerably lower than those demonstrated to have acute toxic effects. For example, concentrations of total alkyl benzenes in heavily polluted urban air typically range from 100 to 200 ppb, compared with phytotoxic thresholds of approximately 5 ppm. Similarly, concentrations in aquatic environments are much lower than the toxicity thresholds to the vast majority of aquatic organisms. Even under severe conditions, when thresholds may be temporarily exceeded, the biological effects are likely to be relatively short-lived. Because the alkyl benzenes are not stored in animal tissues and since they are rapidly metabolized and excreted (see Chapter 5), chronic toxic effects are unlikely. There is no evidence to suggest irreversible or persistent tissue damage following sublethal acute exposures. However, the possible occurrence of more subtle behavioral changes (e.g., avoidance) resulting from exposures to low levels of

alkyl benzenes should not be ignored. Such changes could have serious implications for the continued well-being and integrity of populations of living organisms.

It should be noted, however, that data on biological effects of alkyl benzenes relate almost exclusively to individual species and that no studies appear to have been conducted with either natural or experimental ecosystems. The results of such studies would significantly extend the data base and provide a more complete understanding of the potential environmental effects of alkyl benzenes.

A comprehensive evaluation of the hazards of alkyl benzenes to nonmammalian species is lacking. Particularly evident is the omission of system-level studies, i.e., effects on biological communities or ecosystem functions that cannot be predicted from tests with individual species. The alkyl benzenes should be subjected to a systematic hazard evaluation process according to guidelines suggested by Cairns et al. (1978), Dickson et al. (1979), and the National Academy of Sciences (1975b).

REFERENCES

- Barash, V. A. 1957. The influence of some mineral and organic substances on methane fermentation in sewage sludges. Pp. 105-114 in Vsesoyuz. Nauch.-Issledovatel Inst. Vodosnabzhen., Kanalizats., Gidrotekh. Sooruzhenii i Inzhener. Gidrogeol. Materialy Soveshchaniya 1955. [Chem. Abs. 52:7583i, 1958.]
- Beetle, D. E. 1951. The effect of DDT, triton, and xylene upon the germination of some crop plants. Univ. Wyo. Publ. 15(2): 50-54.
- Benville, P. E., Jr., and S. Korn. 1977. The acute toxicity of six monocyclic aromatic crude oil components to striped bass (Morone saxatilis) and bay shrimp (Crago franciscorum). Calif. Fish Game 63:204-209.
- Berry, W. O., and J. D. Brammer. 1977. Toxicity of water-soluble gasoline fractions to fourth-instar larvae of the mosquito Aedes aegypti L. Environ. Pollut. 13:229-234.
- Berry, W. O., J. D. Brammer, and D. E. Bee. 1978. Uptake of water-soluble gasoline fractions and their effect on oxygen consumption in aquatic stages of the mosquito (Aedes aegypti L.) Environ. Pollut. 15:1-22.
- Bhatt, S. K. 1964. Keeping quality of cut flowers by some chemicals. Sci. Cult. 30:410-412.
- Brenniman, G., R. Hartung, and W. J. Weber, Jr. 1976. A continuous flow bioassay method to evaluate the effects of outboard motor exhausts and selected aromatic toxicants on fish. Water Res. 10:165-169.
- Bringham, G., and R. Kühn. 1959. The toxic effects of waste water on aquatic bacteria, algae, and small crustaceans. Gesund. Ing. 80:115-120. [Chem. Abs. 53:17390g, 1959.]
- Brown, E. R., J. J. Hazdra, L. Keith, I. Greenspan, J. B. G. Kwapinski, and P. Beamer. 1973. Frequency of fish tumors found in a polluted watershed as compared to nonpolluted Canadian waters. Cancer Res. 33:189-198.
- Bruns, V. F., J. M. Hodgson, H. F. Arle, and F. L. Timmons. 1955. The Use of Aromatic Solvents for Control of Submersed Aquatic Weeds in Irrigation Channels. Circular No. 971. U.S. Department of Agriculture, Washington, D.C.

- Cairns, J., Jr., K. L. Dickson, and A. W. Maki, eds. 1978. Estimating the Hazard of Chemical Substances to Aquatic Life. Sponsored by ASTM, Committee D-19 on Water. ASTM Special Technical Publication 657. American Society for Testing and Materials, Philadelphia, Penna. 278 pp.
- Currier, H. B. 1951. Herbicidal properties of benzene and certain methyl derivatives. *Hilgardia* 20:383-406.
- Dallyn, S. L., and R. D. Sweet. 1951. Theories on the herbicidal action of petroleum hydrocarbons. *Proc. Am. Soc. Hortic. Sci.* 57:347-354.
- Denny, F. E. 1926. Hastening the sprouting of dormant potato tubers. *Am. J. Bot.* 13:118-125.
- De Smet, M. J., J. Kingma, and B. Witholt. 1978. The effect of toluene on the structure and permeability of the outer and cytoplasmic membranes of Escherichia coli. *Biochim. Biophys. Acta* 506:64-80.
- Deutscher, M. P. 1974. Preparation of cells permeable to macromolecules by treatment with toluene: Studies of transfer ribonucleic acid nucleotidyltransferase. *J. Bacteriol.* 118(2): 633-639.
- Dickson, K. L., A. W. Maki, J. Cairns, Jr. 1979. Analyzing the Hazard Evaluation Process. Proceedings of a Workshop held in Waterville Valley, New Hampshire, August 14-18, 1978. Water Quality Section, American Fisheries Society, Washington, D.C. 159 pp.
- Donahue, W. H., R. T. Wang, M. Welch, and J. A. C. Nicol. 1977. Effects of water-soluble components of petroleum oils and aromatic hydrocarbons on barnacle larvae. *Environ. Pollut.* 13:187-202.
- Dunstan, W. N., L. P. Atkinson, and J. Natoli. 1975. Stimulation and inhibition of phytoplankton growth by low molecular weight hydrocarbons. *Mar. Biol.* 31:305-310.
- Ezekial, W. N., and J. J. Taubenhaus. 1935. Field trials of pentachloroethane, tetrachloroethane and xylene as affecting Phymatotrichum root rot and host plants. *Phytopathology* 25:16. [Chem. Abs. 29:22892, 1935.]
- Ferguson, J. 1939. The use of chemical potentials as indices of toxicity. *Proc. Roy. Soc. London Ser. B* 127:387-404.

- Ferguson, J., and H. Pirie. 1948. The toxicity of vapours to the grain weevil. *Ann. Appl. Biol.* 35:532-550.
- Folmar, L. C. 1976. Overt avoidance reactions of rainbow trout fry to nine herbicides. *Bull. Environ. Contam. Toxicol.* 15: 509-514.
- Frank, P. A., N. E. Otto, and T. R. Bartley. 1961. Techniques for evaluating aquatic weed herbicides. *Weeds* 9:515-521.
- Funasaka, R., Y. Ose, and T. Sato. 1975. Offensive odor of fish from the Nagara River. III. Aromatic hydrocarbons as one of the offensive-odor substances. *Eisei Kagaku* 21:93-100. [Chem. Abs. 83:173356n, 1975.]
- Gibson, D. T. 1975. Microbial degradation of hydrocarbons. Pp. 667-696 in E. D. Goldberg, ed. *The Nature of Seawater: Report of the Dahlem Workshop on the Nature of Seawater*, Berlin, 1975, March 10-15. Physical and Chemical Sciences Research Report 1. Dahlem Konferenzen, Berlin.
- Grbić, D., and I. Munjko. 1977. Growth and changes of streptomycetes in media with arylalkenes. *Biologia (Bratislava)* 32: 179-186.
- Howell, S. H., and L. L. Walker. 1972. Synthesis of DNA in toluene-treated Chlamydomonas reinhardi. *Proc. Nat. Acad. Sci. U.S.A.* 69:490-494.
- Jackson, R. W., and J. A. DeMoss. 1965. Effects of toluene on Escherichia coli. *J. Bacteriol.* 90:1420-1425.
- Kauss, P. B., and T. C. Hutchinson. 1975. The effects of water-soluble petroleum components on the growth of Chlorella vulgaris Beijerinck. *Environ. Pollut.* 9(3):157-174.
- Kocher, C., and K. B. S. Ascher. 1954. Topical application of organic solvents in houseflies. *Riv. Parassitol.* 15(2): 103-109.
- Korn, S., N. Hirsch, and J. W. Struhsaker. 1977. The uptake, distribution, and depuration of ¹⁴C benzene and ¹⁴C toluene in Pacific herring, Clupea harengus pallasi. *U.S. Nat. Mar. Fish. Serv. Fish. Bull.* 75(3):633-636.
- Lee, R. F., K. Sauerheber, and A. A. Benson. 1972. Petroleum hydrocarbons: Uptake and discharge by the marine mussel Mytilus edulis. *Science* 177:344-346.

- Lerner, H. R., D. Ben-Bassat, L. Reinhold, and A. Polijakoff-Mayber. 1978. Induction of "pore" formation in plant cell membranes by toluene. *Plant Physiol.* 61:213-217.
- McAuliffe, C. D. 1976. Surveillance of the marine environment for hydrocarbons. *Mar. Sci. Commun.* 2:13-42.
- McAuliffe, C. D. 1977b. Evaporation and solution of C_2 to C_{10} hydrocarbons from crude oils on the sea surface. Pp. 363-372 in D. A. Wolfe, ed. *Fate and Effects of Petroleum Hydrocarbons in Marine Organisms and Ecosystems*. Pergamon Press, New York.
- Miller, T. A., D. H. Rosenblatt, J. C. Dacre, J. C. Pearson, and R. K. Kulkarni. 1976. Problem Definition Studies on Potential Environmental Pollutants. IV. Physical, Chemical, Toxicological, and Biological Properties of Benzene; Toluene; Xylenes; and para-Chlorophenyl Methyl Sulfide, Sulfoxide, and Sulfone. (Available from the National Technical Information Service, Springfield, Va., as AD/A-040 435.) Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Md. 95 pp.
- Mitchell, R., S. Fogel, and I. Chet. 1972. Bacterial chemoreception: An important ecological phenomenon inhibited by hydrocarbons. *Water Res.* 6:1137-1140.
- Miwa, T., M. Fujisaki, K. Tanaka, K. Takano, and H. Murakami. 1946. The mechanism of hardening of water-covered sweet potatoes. *Science (Japan)* 16:97-98. [Chem. Abs. 45:1269e, 1951.]
- Moore, W. 1917. Toxicity of various benzene derivatives to insects. *J. Agric. Res.* 9:371-381.
- Morré, D. J., B. J. Rogers, and R. Gamble. 1965. Promotion of plant growth by long chain alcohols and organic solvents. *Phyton (Buenos Aires)* 22:7-12.
- Morrow, J. E., R. L. Gritz, and M. P. Kirton. 1975. Effects of some components of crude oil on young coho salmon. *Copeia* 2:326-331.
- Munjko, I., and D. Grbić. 1977. Influence of styrene and alphas-methylstyrene upon algae and moulds. *Biologia (Bratislava)* 32:173-177.
- Munson, S. C., and J. F. Yeager. 1945. DDT-like effects from injection of other compounds into roaches. *J. Econ. Entomol.* 38:618. [Chem. Abs. 40:12354, 1946.]

- National Academy of Sciences. 1975a. Petroleum in the Marine Environment. Workshop on Inputs, Fates, and the Effects of Petroleum in the Marine Environment, May 21-25, 1973, Airlie, Virginia. National Academy of Sciences, Washington, D.C. 107 pp.
- National Academy of Sciences. 1975b. Principles for Evaluating Chemicals in the Environment. A Report of the Committee for the Working Conference on Principles of Protocols for Evaluating Chemicals in the Environment. Environmental Studies Board, National Academy of Sciences, National Academy of Engineering and Committee on Toxicology, National Research Council. National Academy of Sciences, Washington, D.C. 454 pp.
- North, W. J., K. A. Clendenning, and H. L. Scotten. 1959. The Effects of Waste Discharges upon Kelp. Institute of Marine Resources, University of California, La Jolla, Calif.
- Ogata, M., and Y. Miyake. 1973. Identification of substances in petroleum causing objectionable odour in fish. Water Res. 7:1493-1504.
- Ogata, M., and Y. Miyake. 1979. Disappearance of aromatic hydrocarbons and organic sulfur compounds from fish flesh reared in crude oil suspension. Water Res. 13:75-78.
- Ohmori, S., M. Ikeda, and M. Ogata. 1975. The metabolism and accumulation of petroleum compounds in fish: The side chain oxidation of p-nitrotoluene and p-nitrobenzyl alcohol in liver homogenates of the rat and eel. Physiol. Chem. Phys. 7:477-480.
- Pagano, G., A. Esposito, G. G. Giordano, and B. E. Hagström. 1978. Embryotoxic and teratogenic effects of styrene derivatives on sea urchin development. Scand. J. Work Environ. Health 4(Suppl. 2):136-141.
- Pickering, Q. H., and C. Henderson. 1966. Acute toxicity of some important petrochemicals to fish. J. Water Pollut. Control Fed. 38:1419-1429.
- Potera, G. T. 1975. The effects of benzene, toluene and ethylbenzene on several important members of the **estuarine** ecosystem. Ph.D. dissertation, Lehigh University, Bethlehem, Penna. 117 pp.
- Price, K. S., G. T. Waggy, and R. A. Conway. 1974. Brine shrimp bioassay and seawater BOD of petrochemicals. J. Water Pollut. Control Fed. 46:63-77.

- Pringsheim, E. G. 1930. Untersuchungen über Samenquellung.
1. Mitteilung. Die Abhängigkeit der Quellung von der
Beschaffenheit der Samen und von Medium. *Planta* 11:
528-581.
- Sabalitschka, Th., and J. Preuss. 1954. Action of toluene
on bacteria. *Deut. Apoth.-Ztg. ver. Süddeut. Apoth.-Ztg.* 94:
1226-1228. [Chem. Abs. 49:8389d, 1955.]
- Sauer, T. C., Jr., W. M. Sackett, and L. M. Jeffrey. 1978. Vo-
latile liquid hydrocarbons in the surface waters of the Gulf
of Mexico. *Marine Chemistry* 7:1-16.
- Shelford, V. E. 1917. An experimental study of the effects of
gas waste upon fishes, with especial reference to stream
pollution. III. *State Lab. Nat. Hist. Bull.* 11:381-412.
- Silva, M. T., J. C. F. Sousa, and G. Balassa. 1978. Ultrastruc-
tural effects of chemical agents and moist heat on Bacillus
subtilis. I. Effects on vegetative cells. *Ann. Microbiol.*
(Paris) 129B:363-375.
- Slifer, E. M. 1946. The effects of xylol and other solvents on
diapause in the grasshopper egg; together with a possible
explanation for the action of these agents. *J. Exp. Zool.*
102:333-356.
- Stoss, F. W., and T. A. Haines. 1979. The effects of toluene on
embryos and fry of the Japanese medaka Oryzias latipes with a
proposal for rapid determination of maximum acceptable toxicant
concentration. *Environ. Pollut.* 20:139-148.
- U.S. Environmental Protection Agency. 1978. In Depth Studies on
Health and Environmental Impacts of Selected Water Pollutants.
Contract No. 68-01-4646. U.S. Environmental Protection Agency,
Washington, D.C.
- U.S. Environmental Protection Agency. 1979. Toluene. Ambient
Water Quality Criteria. Criteria and Standards Division,
Office of Water Planning and Standards, U.S. Environmental
Protection Agency, Washington, D.C.
- Vas, K. 1953. (English summary) .On the mechanism of antimicrobial
action: Interference with the cytoplasmic membrane. *Agrokem.*
Talajtan 2:1-16.
- Wallen, I. E., W. C. Greer, and R. Lasater. 1957. Toxicity to
Gambusia affinis of certain pure chemicals in turbid waters.
Sewage Ind. Wastes 29:695-711.

- Walsh, D. F., J. G. Armstrong, T. R. Bartley, H. A. Salman, and P. Frank. 1977. Residues of Emulsified Xylene in Aquatic Weed Control and Their Impact on Rainbow Trout. Report No. REC-E-75-11. (Available from the National Technical Information Service, Springfield, Va., as PB-267 270.) Bureau of Reclamation Engineering and Research Center, Denver, Colo. 24 pp.
- Woldringh, C. L. 1973. Effects of toluene and phenethyl alcohol on the ultrastructure of Escherichia coli. J. Bacteriol. 111: 1359-1361.
- Young, L. Y., and R. Mitchell. 1973. Negative chemotaxis of marine bacteria to toxic chemicals. Appl. Microbiol. 25: 972-975.

CHAPTER 9

SUMMARY AND RECOMMENDATIONS FOR FUTURE RESEARCH

The data and conclusions presented in this report relate only to the six compounds reviewed in this document, i.e., toluene, the xylenes, ethylbenzene, cumene, styrene, and styrene oxide. These data suggest that we have a generally good working understanding of the toxicology of the alkyl benzenes that occur most commonly in the environment. However, they are inadequate for estimating risk. To expand our understanding of these compounds, further research should be conducted in the following areas: the generation, occurrence, and control of alkyl benzene emissions in the environment; the environmental fate and biological effects of alkyl benzenes; the mechanisms of toxicity of the common alkyl benzenes as well as the other alkyl benzenes, i.e.:

- allylbenzene,
- cyclohexylbenzene,
- o-, m-, and p-diisopropylbenzene,
- o-, m-, and p-divinylbenzene,
- dodecylbenzene,
- ethynylbenzene
- hexamethylbenzene,
- n-, sec-, and tert-pentylbenzene,
- pentamethylbenzene,
- n-propylbenzene,
- 1,2,4,5-tetramethylbenzene,
- 1,2,4- and 1,3,5-triethylbenzene, and
- 1,2,3-, 1,2,4-, and 1,3,5-trimethylbenzene;

and, of fundamental importance, the differences in toxicity between the alkyl benzenes and benzene.

ALKYL BENZENES IN THE ENVIRONMENT

Summary

Alkyl benzenes are emitted into the atmosphere as air pollutants primarily from solvents, from gasoline usage, and, to a lesser extent, from the use of diesel fuel. Other sources, most of which are industrial, contribute a far smaller amount nationally, but such sources may be significant locally. Urban levels of toluene normally range from 1 to 10 ppb but may be either 10 times lower or 5 times higher than these values. Because the higher molecular weight compounds are used in smaller amounts, they are found in lower concentrations in the environment.

Alkyl benzenes currently comprise between 25% and 40% of non-methane hydrocarbons in urban and suburban atmospheres. Although total atmospheric hydrocarbons have declined significantly in some areas during the last 10 to 15 years, this trend may not continue. Furthermore, it is likely that alkyl benzenes will contribute a larger proportionate share of the total hydrocarbons in the future.

Alkyl benzenes apparently have a minimal potential for direct toxicity at ambient levels, but because they comprise a significant percentage of nonmethane hydrocarbons in urban and suburban atmospheres, they are likely to have a considerable influence on the environment as a result of their chemical breakdown in the atmosphere. Like other hydrocarbons, they cause the photooxidation of atmospheric nitric oxide to nitrogen dioxide, which is followed by the formation of ozone--one of the major air pollutants of concern in the nation today. Since ozone is produced in the atmosphere as a secondary air pollutant, rather than emitted directly, its control is difficult.

It should also be noted that alkyl benzenes yield large amounts of peroxy nitrates, another class of air pollutants, when they decompose. Several other decomposition products have been identified as well, but most of them disappear from the gas phase in laboratory experiments.

Recommendations

Environmental Sources. Although it is known that automobile exhausts and evaporating gasoline and solvents are the major sources of alkyl benzenes in the environment, more information is required to pinpoint the relative contribution of these major sources to the environment.

Minor amounts of alkyl benzenes are emitted into water from the exhausts of boats or ships, petroleum spills, seepage, or runoffs. It is important that we learn more about the consequences of spills of oil and petroleum products. The committee was disappointed to learn that during the large oil spill emanating from the uncapped well in the Gulf of Mexico, no monitoring data were collected by either the U.S. Environmental Protection Agency or the State of Texas as the oil approached the Texas shore. Studies in these areas, coupled with an evaluation of the effects of the spills on aquatic life, would be invaluable for our understanding of the effects of mixtures of these compounds in the environment and for obtaining estimates of human exposure. Levels of alkyl benzenes must be monitored under these circumstances to derive an estimate of human exposure to alkyl benzenes. To accomplish this effectively, research should be directed toward developing improved methods for identifying the specific compounds and highly sensitive, mobile instruments that can be expeditiously applied to this effort.

The future will find us facing the inevitably greater use of coal as a source of fuel, either directly or by virtue of its conversion to liquid fuels. Because coal contains large amounts of alkyl benzenes, it will be important to monitor and consider the possible control of the release of these compounds during the processing of coal.

Atmospheric Photooxidation. Cost-effective ozone controls will require a thorough understanding of the mechanism whereby individual atmospheric hydrocarbons promote ozone formation. Alkyl benzenes are recognized as an important class of hydrocarbons in ozone formation, especially from the standpoint of their reactivity and ambient concentrations. Yet, their chemistry is the least understood and is not included in current models for ozone regulation.

Because alkyl benzenes yield large quantities of peroxy nitrates and lesser amounts of other decomposition products, they may be important contributors to the formation of some atmospheric aerosol. These effects cannot be assessed until the physical and chemical nature of the oxidation products have been ascertained. Future work must involve the development of compound-specific models for atmospheric chemical reactivity, nitric oxide photooxidation, and ozone formation. This will entail the identification of the major intermediate oxidation products and measurement of their own reactivity. It is likely that the chemistry involved will be influenced strongly by transformation of many of the products from the gas phase to the aerosol phase or their adsorption on the side walls of vessels. Studying these processes in the laboratory or in the atmosphere will be difficult but may prove useful for developing models for control of air pollutants.

METABOLISM

Summary

Nonmammals. The limited information in the literature indicates that alkyl benzenes can be metabolized by a variety of nonmammalian species. The metabolic pathways in insects appear to be quite similar to those reported for mammals. Because the microsomal oxidase systems in a wide variety of vertebrate and invertebrate organisms are similar, the metabolic pathways in fish, birds, reptiles, etc., should also prove to be qualitatively similar, i.e., the major pathways are likely to involve initial oxidation of the alkyl moiety of the compound and subsequent conjugation prior to excretion.

In contrast, metabolism by microbial species and by higher plants involves cleavage of the aromatic ring in addition to side-chain oxidation and leads ultimately to the formation of a variety of straight-chain acids, which can be utilized as a source of carbon for energy production. As a result, it may be assumed that alkyl benzenes will be degraded rapidly by microbial species and that they will probably not accumulate to any significant extent under most environmental conditions.

Mammals. The principal metabolic pathways of the alkyl benzenes in mammals have been known for many years. Despite the plethora of studies on the metabolism of these substances, few studies have been designed to determine whether any of their biological effects are mediated by their metabolites. Indeed, the studies on the mutagenic effects of styrene epoxide on Salmonella typhimurium provide the only clear evidence that any of the intermediary metabolites of these compounds are toxic. Unfortunately, it is not clear whether or not mutagenic effects of styrene observed in these studies were due solely to styrene epoxide. Without such knowledge, it is difficult to evaluate the ways in which metabolism affects the toxicity of the alkyl benzenes or the extent to which differences in the incidence or severity of toxicity among species is due to interspecies differences in metabolism.

Recommendations

More detailed studies should be conducted to evaluate the metabolic pathways and rate of metabolism of alkyl benzenes in birds, fish, and other nonmammalian species.

Unless there is some future indication that these substances represent a major threat to the health of humans and that their

toxicity is mediated through the formation of metabolites, less emphasis should be placed on studies of their metabolism in mammals.

Since the metabolism of the other alkyl benzenes is not completely understood, metabolic studies in both mammalian and nonmammalian species should be conducted for the compounds listed on page 373.

TOXICITY

Summary

Nonmammalian Species. An evaluation of the data from the relatively few studies that have been conducted in nonmammalian species indicates that high concentrations of alkyl benzenes produce toxic effects in a variety of living organisms. Although chronic studies have not been conducted, most of the toxicity appears to be acute and results from a rather nonspecific action causing a breakdown in the structure and functional integrity of biological membranes. The evidence suggests that the alkyl benzenes can be classified within the large group of nonspecific narcotic agents and that their action is related more to their physical or colligative properties than to the presence of specific structural characteristics. Consequently, the biological activity of the alkyl benzenes can be expected to increase with the number and/or size of the alkyl substituents, and their acute effects are likely to be reversible unless exposure involves extremely high concentrations, which result in a total disruption of membrane function and a consequent breakdown in cell organization. This type of toxic action will probably be observed in all types of living organisms.

Except under unusually severe circumstances, e.g., near major spills or other sources of pollution, concentrations of alkyl benzenes in the environment are considerably lower than those demonstrated to have acute toxic effects. For example, concentrations of total alkyl benzenes in heavily polluted urban air typically range from 100 to 200 ppb, compared with phytotoxic thresholds of approximately 5 ppm. Similarly, concentrations in aquatic environments are much lower than the toxicity thresholds to the vast majority of aquatic organisms. Even under severe conditions, when thresholds may be temporarily exceeded, the biological effects are likely to be relatively short-lived. Because the alkyl benzenes are not stored in animal tissues and since they are rapidly metabolized and excreted (see Chapter 5),

chronic toxic effects are unlikely. There is no evidence to suggest irreversible or persistent tissue damage following sub-lethal acute exposures. However, the possible occurrence of more subtle behavioral changes (e.g., avoidance) resulting from exposures to low levels of alkyl benzenes should not be ignored. Such changes could have serious implications for the continued well-being and integrity of populations of living organisms.

Mammals. The naturally occurring alkyl benzenes covered in this report--toluene, ethylbenzene, cumene, and xylenes--all produce narcosis. The LD₅₀ values for these compounds are high, indicating that the toxicity of the alkyl benzenes is relatively low. Glue sniffing, often involving inhalation of toluene, has become a well-known problem. It has been associated with the "sudden sniffing death" syndrome and may be related to cardiac arrhythmias caused by toluene.

Studies of xylene and toluene indicate that the alkyl benzenes considered in this report have a low order of toxicity. Although people exposed occupationally may be at some risk, there appears to be little danger of adverse effects on the general population as a result of current or projected ambient levels of exposure. In the absence of quantitative toxicological data concerning the effects and mechanisms of action of individual alkyl benzenes and combinations thereof, it is reasonable to assume that the actions of combinations of two or more of these substances on the nervous system are at least additive.

Evaluations of the teratogenic potential of toluene, xylene, ethylbenzene, and cumene indicate that they may have mild embryotoxic effects. The natural alkyl benzenes are not mutagenic in the Ames test, but toluene increases chromosomal aberrations in rats. However, these aberrations were not observed in printers exposed to toluene for 15 years. The carcinogenic potential of toluene, the xylenes, ethylbenzene, and cumene has not been examined via long-term bioassays.

Clinical exposure to alkyl benzenes occurs mainly among adolescents through deliberate inhalation of "glue" or solvents, which commonly contain toluene. Although sudden death due to solvent sniffing has been reported in a number of cases, and neurological, hematological, renal, and metabolic effects have been associated with glue sniffing, it appears that alkyl benzenes play a relatively minor role in nonfatal toxicity due to solvent sniffing. Furthermore, the variable composition of the glue and the presence of a number of other hydrocarbons besides alkyl benzenes cloud the interpretation of the data.

Epidemiological studies of toluene, ethylbenzene, cumene, and the xylenes offer few data and are inconclusive.

Styrene and styrene oxide are the only synthetic alkyl benzenes considered in this report. Styrene liquid and vapor are irritating to the eyes, nose, throat, and skin. Acute exposure to high concentrations of styrene may produce irritation of the mucous membranes of the upper respiratory tract, nose, and mouth, followed by symptoms of narcosis and muscular contractions due to paralysis of the respiratory center. Styrene (rat oral LD₅₀, 5.0 g/kg body weight) is more acutely toxic than benzene (LD₅₀, 5.6 g/kg body weight) and toluene (LD₅₀, 7.0 g/kg body weight) but less toxic than xylene (LD₅₀, 4.3 g/kg body weight). The acute toxicity of styrene appears to be similar to that of other aromatic hydrocarbons such as toluene, xylenes, and ethylbenzene. The urinary metabolites of styrene are all less toxic than styrene, and therefore may not contribute to its acute toxicity. Pretreatment of rats with phenobarbital enhances selectively the metabolism of styrene to styrene oxide, whereas the administration of 2-diethylaminoethyl-2,2-diphenylvalerate hydrochloride (SKF 525-A) depresses the metabolism. These effects may play a vital role by altering the toxicity of styrene as well as by converting the compound to a more toxic and mutagenic product, namely styrene oxide. Reduced glutathione in the liver plays a central role in the development of cell damage by styrene.

The most apparent hazard to health from styrene oxide resides in its ability to cause irritation and hypersensitization of the skin. The effects may result from single or repeated contacts with undiluted material and solutions as dilute as 1%. A comparison of rat oral LD₅₀'s obtained from inhaled and intraperitoneal doses of styrene oxide and styrene indicates that styrene oxide is 1.5 to 5 times more toxic than styrene. A comparison of the binding parameters of styrene oxide in interactions with uninduced microsomes and those induced by phenobarbital and 3-methylcholanthrene from mouse liver and kidney indicates that the binding of styrene oxide is catalyzed by more than one type of P-450 hemoprotein, but predominantly by phenobarbital-induced cytochrome P-450.

Objective evidence of the toxicity of styrene to the central nervous system in animals has not been found to result from exposures to 300 ppm or less. Experimental and occupational exposures of humans have shown that eye, nose, and throat irritation occur at levels of 200 ppm or more and that subtle changes in psychological test performance, electroencephalograms, and peripheral nerve conduction may result from chronic exposure to levels of 50 ppm or less. There are no data on the neurotoxicity of styrene oxide.

Styrene was found to be less embryotoxic than styrene oxide. Both compounds cause malformations in developing chicks. Trichloropropylene oxide (1,2-epoxy-3,3,3-trichloropropane), an inhibitor of epoxide hydratase, has some synergistic effect on the embryotoxicity of styrene and styrene oxide.

Contradictory results have been obtained from Ames Salmonella microsome assays intended to evaluate the mutagenic potential of styrene. In contrast, styrene oxide has been found to cause mutations with or without the presence of rat liver microsome (i.e., with or without metabolic activation) in histidine-requiring Salmonella strains TA100 and TA1535 (revertable to prototrophy by base-pair substitutions). Styrene oxide was also found to be mutagenic in a yeast system, but results from the host-mediated assay were inconclusive. Both styrene and styrene oxide have been reported to have clastogenic activity.

The only bioassay conducted thus far to determine the carcinogenicity of styrene is inconclusive. However, one bioassay has indicated that styrene oxide may be carcinogenic. It is of interest that this compound is also a substrate for the mixed-function oxidase enzyme system. Thus, it may be questioned whether styrene oxide is a reactive metabolite leading to carcinogenesis or whether it is further converted to the ultimate carcinogen.

The epidemiological studies of exposure to styrene indicate that exposure to high concentrations is associated with pre-narcotic symptoms and an increase in the number of symptoms in the lower respiratory tract; however, the authors did not believe that these were clinically significant. A study of plastics workers was generally negative; however, it did suggest a need for further psychomotor, behavioral, and pulmonary function testing. Two mortality studies of workers in the styrene-polystyrene industry were negative.

Recommendations

Knowledge of the biochemical mechanisms of action of the alkyl benzenes is still quite fragmentary. Therefore, decisions concerning safe levels of exposure must be recognized as "best judgments" that lack any great degree of precision until future studies supply more complete information.

Nonmammalian Species. As a consequence of the ubiquitous environmental distribution of the alkyl benzenes, a large number of aquatic and terrestrial species are exposed. Although the data accumulated thus far do not indicate serious toxicological effects in these species except at high dosage levels, detailed studies of possible chronic effects of environmental levels of alkyl benzenes should be conducted in individual species. Such effects might include not only those leading to death but also more subtle effects such as behavioral modifications that cause organisms to avoid contaminated areas. There is only limited information on the direct toxicity of alkyl benzenes to fish and other aquatic organisms, plants, microbes, and, to a

extent, insects. Data on birds and wild mammals are virtually nonexistent, and little is known of the toxicity of possibly reactive intermediates formed under environmental conditions.

It should be noted, however, that data on biological effects of alkyl benzenes relate almost exclusively to individual species and that no studies appear to have been conducted with either natural or experimental ecosystems. The results of such studies would significantly extend the data base and provide a more complete understanding of the potential environmental effects of alkyl benzenes.

A comprehensive evaluation of the hazards of alkyl benzenes to nonmammalian species is lacking. Particularly evident is the omission of system level studies, i.e., effects on biological communities or ecosystem functions that cannot be predicted from tests with individual species. The alkyl benzenes should be subjected to a systematic hazard evaluation process.

Mammals. The main biological effect of the alkyl benzenes in mammals appears to be their depressant activity on the central nervous system. Clearly, the neurotoxicity of the alkyl benzenes must be further understood. Moreover, the reason for the differences between the neurotoxicity of the hexanes and these compounds should be further delineated. It appears that hexane undergoes metabolic activation to a diketone, which is the ultimate neurotoxin, whereas the alkyl benzenes probably exert their neurotoxic effects without metabolic activation. Nevertheless, it would be worthwhile to study the neurotoxicity of these compounds in low-dose, longer-term experiments in which metabolism can be evaluated during the development of the disease and its progress related to the formation of specific metabolites.

As summarized above, of the alkyl benzene compounds described in this report, only styrene and styrene oxide appear to have the potential to cause genetic damage in humans. Styrene oxide appears to be mutagenic and embryotoxic, but the data on styrene are less well defined. If it were established that styrene oxide is the toxic form of styrene, we could be more predictive of effects on humans caused by styrene in the environment. Since the standard 2-year bioassay for carcinogenesis in rats and mice for styrene produced unclear results, there is a need to develop a different strategy for studying the carcinogenic potential of styrene and its oxide. Studies of carcinogenicity should also be considered for the other compounds discussed in this report.

Studies have suggested that exposure of humans to high

respiratory tract; however, some investigators did not believe that these were clinically significant. These studies should be extended.

At the outset, the committee voted to study only toluene, the xylenes, ethylbenzene, cumene, styrene, and styrene oxide mainly because there is very little information on the toxicity of the other alkyl benzenes. It therefore recommends that studies be conducted to determine the toxicology of the compounds listed on page 373.

Comparison of the toxicity of the alkyl benzenes with that of benzene may be helpful in determining the types of studies needed to define the toxicological mechanisms of these compounds. The acute depressant activity of the alkyl benzenes on the central nervous system is shared by benzene (Snyder and Kocsis, 1975). Of greater interest within the context of this report are the effects of lower doses at longer exposures. The chronic toxicity of benzene leads to depression of bone marrow, which may result in decreases in the circulating levels of red cells, white cells, and/or platelets. In the most severe cases, pancytopenia results from bone marrow aplasia, and acute myelogenous leukemia has also been observed occasionally (Vigliani and Forni, 1969). Thus, damage of bone marrow by benzene can lead to a cessation of normal medullary cell proliferation, but occasionally cells modified by carcinogenesis can escape the inhibitory effects of benzene and initiate leukemia. It must be emphasized that there is no indication that any of the alkyl benzenes described in this report are leukemogenic nor is there any substantial evidence that the alkyl benzenes are bone marrow depressants. Nonetheless, studies on these subjects should be extended to supplement the incomplete data base. Although some evidence indicates that toluene is not a bone marrow depressant (Andrews et al., 1977), further studies of the possible effects of that compound as well as ethylbenzene, cumene, the xylenes, styrene, and styrene oxide on bone marrow should be pursued.

There have been no studies designed specifically to determine the reason for the differences between the effects of benzene and those of alkyl benzenes. These dissimilarities are probably related to differences in metabolic pathways because benzene-induced bone marrow toxicity results from the production of an as yet unidentified toxic metabolite (Andrews et al., 1977; Sammett et al., 1979). The U.S. Environmental Protection Agency (1978) has suggested that likely candidates for this metabolite include benzene oxide, catechol, and hydroquinone, or the corresponding semiquinones. There have been no studies of a similar nature involving the alkyl benzenes. Furthermore, it is imperative to look at the alkyl benzenes not considered in this report since their effects on marrow have not been evaluated.

INTERACTIONS WITH OTHER CHEMICALS

Although alkyl benzenes alone appear to be low-potency toxicants, few studies relate to the interaction of alkyl benzenes with other types of chemicals. Therefore, studies in which animals are given both a specific alkyl benzene plus other specific chlorinated hydrocarbons or alkanes such as hexane would be of value. The alterations in toxicity as well as in metabolism should be pursued.

PRIORITIES

Although all of the areas discussed above require further research to enhance our understanding of the occurrence, metabolism, and effects of alkyl benzenes, the committee agrees that the following areas should receive the highest priority:

- The mechanisms of alkyl-benzene-induced neurotoxicity should be examined.
- The metabolism and chronic effects of alkyl benzenes in non-mammalian species should be studied; tests should be conducted to evaluate possible effects of alkyl benzenes at the system level, i.e., effects on biological community or ecosystem functions.
- To resolve some of the major uncertainties regarding the fate of alkyl benzenes in the atmosphere, further research should be conducted on the nature and structure of the products formed, the production of condensed versus gaseous products, and the specific influences that the alkyl benzenes have on ozone, peroxy nitrates, and other oxidants.

REFERENCES

- Andrews, L. S., E. W. Lee, C. M. Witmer, J. J. Kocsis, and R. 1977. Effects of toluene on the metabolism, disposition and hematopoietic toxicity of [³H]benzene. *Biochem. Pharmacol.* 293-300.
- Sammett, D., E. W. Lee, J. J. Kocsis, and R. Snyder. 1979. Partial hepatectomy reduces both metabolism and toxicity of benzene. *J. Toxicol. Environ. Health* 5:785-792.
- Snyder, R., and J. J. Kocsis. 1975. Current concepts of chronic benzene toxicity. *Crit. Rev. Toxicol.* 3:265-288.
- U.S. Environmental Protection Agency. 1978. Assessment of Health Effects of Benzene Germane to Low-Level Exposure. Office of Health and Ecological Effects, U.S. Environmental Protection Agency, Washington, D.C. 112 pp.
- Vigliani, E. C., and A. Forni. 1969. Benzene, chromosome changes and leukemia. *J. Occup. Med.* 11:148-149.